CONTENTS

The American Journal of Medicine

Vol. XV AUGUST, 1953 No. 2

Editorial

Shotgun Antianemic Therapy . . . . . MAXWELL M. WINTROBE 141

Clinical Studies

Transposed Pulmonary Veins. A Correlation of Clinical and Cardiac Catheterization Data

DAVID C. LEVINSON, GEORGE C. GRIFFITH, RICHARD S. COSBY, WILLARD J. ZINN, GEORGE JACOBSON, SIM P. DIMITROFF AND ROBERT W. OBLATH 143

Since the clinical, catheterization and angiocardiographic features of transposition of the pulmonary veins are still rather obscure, this detailed presentation of ten patients is of unusual interest. The cases include four patients with partial pulmonary vein transposition, two with complete transposition (and atrial septal defect) and six in whom pulmonary vein transposition was a minor part of a more complex anomaly. Diagnosis is not possible without recourse to cardiac catheterization and angiocardiography.

Diagnosis of Overriding Aorta. With Special Reference to Circulation Time Tests

ALVIN J. GORDON, RICHARD P. LASSER, HOWARD L. MOSCOVITZ, SIGMUND A. BRAHMS AND FREDERICK H. KING 158

The recognition of overriding aorta, and estimation of the degree of overriding, has become a matter of considerable practical importance since the development of surgical correction of congenital anomalies of the heart. It happens that this problem also presents unusual difficulties. The discussion in this paper is, therefore, timely and important.

The Influence of Age, Anesthesia and Cerebral Arteriosclerosis on Cerebral Vascular Activity to CO_2 . . . . . JAMES F. SCHIEVE AND WILLIAM P. WILSON 171

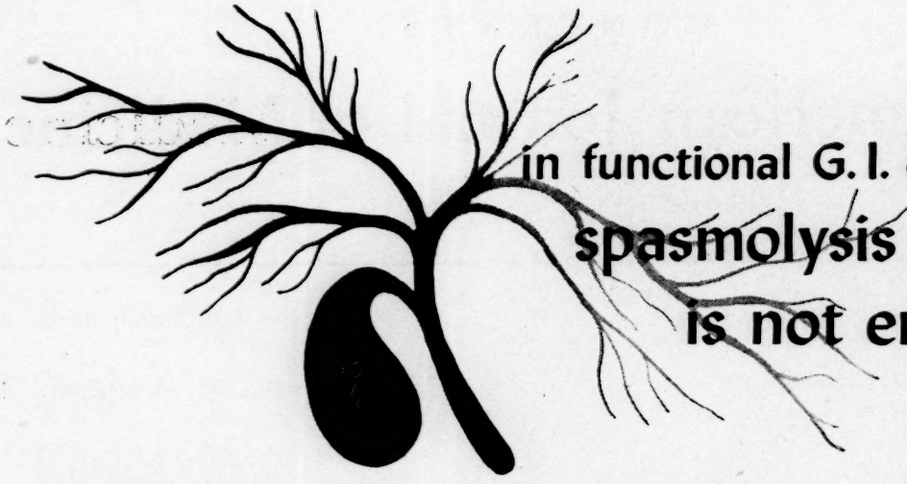
This study is an attempt to detect diffuse sclerosis of the cerebral vessels before a stroke or other evidence of cerebral dysfunction occurs, using as a criterion the effect of inhalation of 5 per cent or 7 per cent CO_2 on cerebral blood flow and A-VO_2 difference. The attempt was only partially successful but indicates the usefulness of this approach.

Tests for So-called Capillary Fragility of the Skin and the Significance of Positive Tests in Vascular Disease

LAURENCE E. HINES, JAMES CATLIN AND DONALD L. KESSLER 175

The authors discuss critically the loose use of the term, positive capillary fragility, and the crude methods of measurement available. Their findings in normal subjects and in patients with vascular

Contents continued on page 5



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CONTENTS

The American Journal of Medicine

Vol. XV AUGUST, 1953 No. 2

Contents continued from page 3

disease, notably in association with diabetes, are summarized. In the last group the correlation of positive capillary fragility with spontaneous retinal hemorrhages is noteworthy.

Chronic Hyperosmolarity of the Body Fluids with a Cerebral Lesion Causing Diabetes Insipidus and Anterior Pituitary Insufficiency
WILLIAM W. ENGSTROM AND ALBERT LIEBMAN 180

In a report of unusual interest in reference to regulation of osmolarity of the body fluids, the authors describe a patient with diabetes insipidus and anterior pituitary insufficiency who regularly exhibited marked hypernatremia and hyperchloremia. The effects of cortisone and pitressin administration are noted in this patient and in two others with diabetes insipidus not associated with hyperosmolarity of extracellular fluid. The findings are consistent with current suspicions that the regulatory role of cerebral centers on normal and abnormal salt and water distribution has not been sufficiently appreciated.

Diabetic Nephropathy. Kidney Biopsy and Renal Function Tests
CLAUS BRUN, HARALD GORMSEN, TAGE HILDEN, POUL IVERSEN AND FLEMMING RAASCHOU 187

The authors here apply the kidney biopsy method to study of the still confused and controversial problem of the nature, significance and specificity of Kimmelstiel-Wilson lesions in diabetic nephropathy. Biopsies were obtained in twelve diabetic subjects; in six there was diffuse hyalinization of the basement membranes, in four there were both diffuse and nodular changes, in one there was complete hyalinization of the glomeruli with nodular changes, and one kidney appeared to be normal. The method would seem to afford an additional means for diagnosis and investigation of this intriguing anomaly.

Needle Biopsy of the Kidney. A Report of Five Cases of Multiple Myeloma
HENRY P. GREENWALD, GERALD J. BRONFIN AND OSCAR AUERBACH 198

The authors present a simplified technic for Vim-Silverman needle biopsy of the kidney and applied the method, without incident, to five cases of multiple myeloma. Apart from the excellent sections so obtained, no noteworthy findings were made. There does not seem to be anything specific about the kidney changes in multiple myeloma, even in the presence of profound renal impairment, which therefore remains of obscure pathogenesis.

Needle Biopsy of the Liver. IV. Relationship of Clinical and Laboratory Findings to Histologic Structure in 100 Cases of Portal Cirrhosis
EDWARD M. SCHNEIDER, JEROME R. BERMAN, EDWARD A. GALL AND LEON SCHIFF 207

Contents continued on page 7

Which aged patient has PA...?

Pernicious anemia is basically a disease of older people. Although none of the aged patients depicted here may have pernicious anemia, it is very likely that all of them have deficient secretion of intrinsic factor, which in extreme cases would result in pernicious anemia. Among the many functions of the human organism which slow down as we advance in age is the stomach's secretion of intrinsic factor. Assure a full quota of intrinsic factor and its essential partner, vitamin B_{12}, for your aged patients by prescribing Bifacton. Only two tiny Bifacton tablets constitute a full U.S.P. anti-anemia unit, sufficient for maximal daily replacement of intrinsic factor and vitamin B_{12}.

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CONTENTS

The American Journal of Medicine

Vol. XV AUGUST, 1953 No. 2

Contents continued from page 5

From this study of cirrhosis, in which it is assumed that the degree of over-all "activity" of the pathologic process and the extent of fibrosis can be reliably assayed in a needle biopsy specimen, the authors conclude that there is no good correlation between the histologic findings and the usual clinical and laboratory criteria. It is not altogether clear which method of assay is deficient.

Paraplegia and Secondary Amyloidosis. Report of Six Cases
WILLIAM NEWMAN AND ABRAHAM S. JACOBSON 216

This study makes clear that among the complications that plague the paraplegic, secondary amyloidosis, the result of extensive associated infection, is included. Large, persistent decubitus ulcers, refractory infections of the urinary tract and osteomyelitis contribute to the development of amyloidosis, the first probably more significantly than has been appreciated.

Review

Varicella Encephalitis
EMANUEL APPELBAUM, MORTON H. RACHELSON AND VERA B. DOLGOPOL 223

The authors summarize a quite unique experience with varicella encephalitis, comprising fifty-nine cases observed over many years. They analyze their data concerning clinical manifestations, spinal fluid findings, prognosis (based on prolonged follow-up in thirty-three patients) and treatment. The mortality rate was 5 per cent and the vast majority of patients escaped without sequelae. This experience therefore indicates that encephalitis is not quite the dread complication of varicella it is generally reputed to be.

Seminars on Neuromuscular Physiology

Some Aspects of the Pharmacology of Neuromuscular Function
WALTER F. RIKER, JR. 231

In this thorough discussion of the problems of neuromuscular function from the point of view of the pharmacologist, Dr. Riker begins with a consideration of the mechanisms of action of acetylcholine and other quaternary amines. There follows a detailed description of blockade of neuromuscular transmission by such agents as curare and an account of the effects of the anti-cholinesterases, with an analysis of their active groups and possible mechanisms of action. The whole provides an excellent introduction to this important area of investigation.

Contents continued on page 9

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Vol. XV AUGUST, 1953 No. 2

Contents continued from page 7

Conference on Therapy

Some Therapeutic Applications of Vasodilating Agents 250

Conferences on Therapy (Cornell University Medical College)—Evaluation of the usefulness of vasodilating agents in the treatment of peripheral vascular disease has not, in the medical literature, been conspicuously critical or well founded. It is therefore especially helpful to have this subject bandied back and forth between clinician and pharmacologist, as in the present Conference. Except for very few agents, among them priscoline, significant dilatation of the peripheral vasculature apparently is not readily accomplished. The pros and cons of management by these and other agents are discussed with vigor.

Clinico-pathologic Conference

Differential Diagnosis of Chest Pain Terminating Fatally 258

Clinico-pathologic Conference (Washington University School of Medicine)—This conference deals informatively and interestingly with a problem that is a matter of daily experience in ordinary medical practice. The discussion revolves around points of immediate interest to every physician.

Case Reports

Werner's Syndrome. With a Report of Two Cases

GLENN W. IRWIN AND PAULA B. WARD 266

A straightforward review of what is known of Werner's syndrome, with an account of two additional interesting examples.

Unusual Thoracic Manifestations in Filariasis Due to Loa Loa. Results of Treatment with Hetrazan and Naphuride Sodium

SAMUEL H. MADELL AND CLIFFORD L. SPINGARN 272

An interesting and well studied case, with a noteworthy therapeutic result.

Advertising Index on 3rd Cover

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Bibliography:

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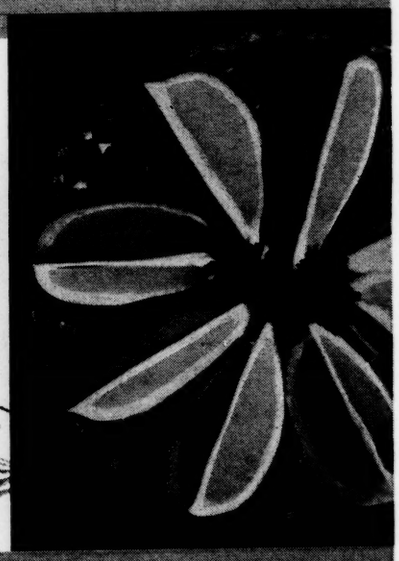

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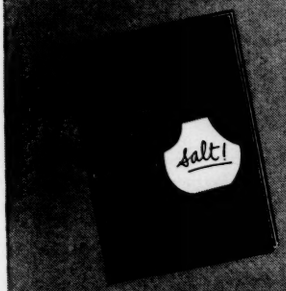

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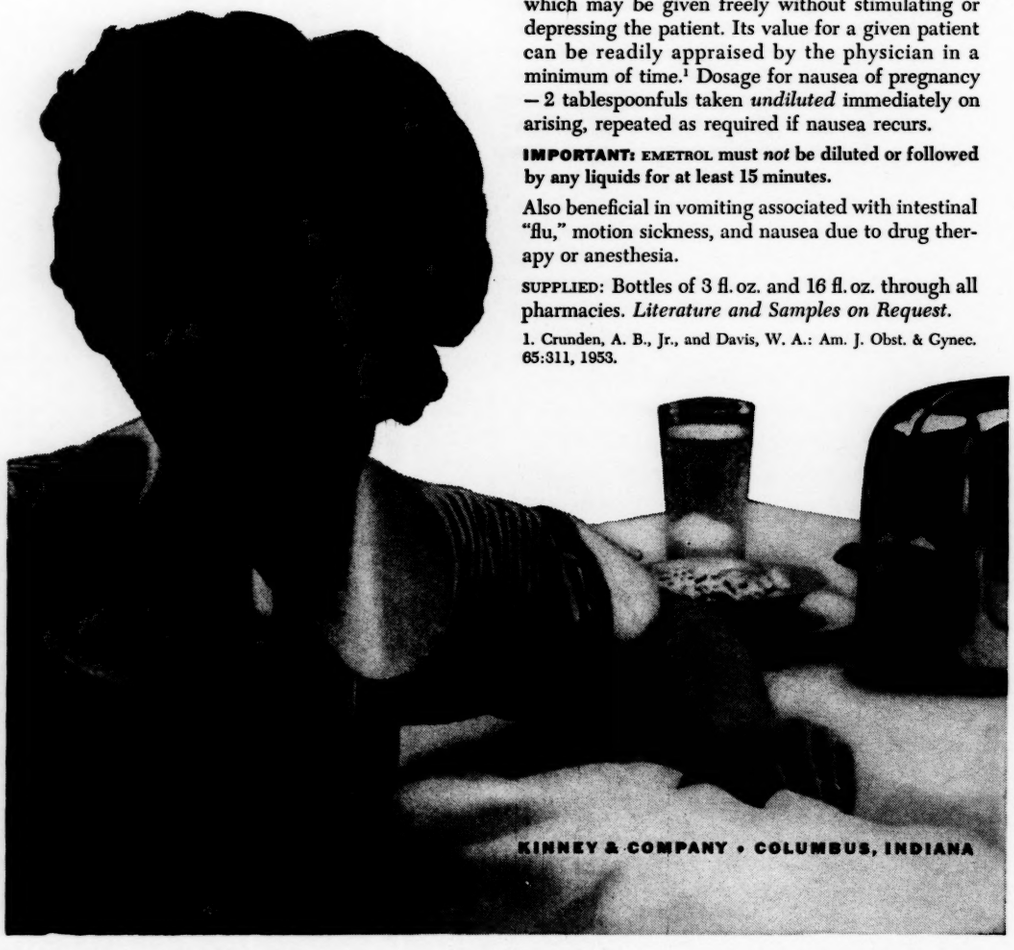
1. Crunden, A. B., Jr., and Davis, W. A.: Am. J. Obst. & Gynec. 65:311, 1953.



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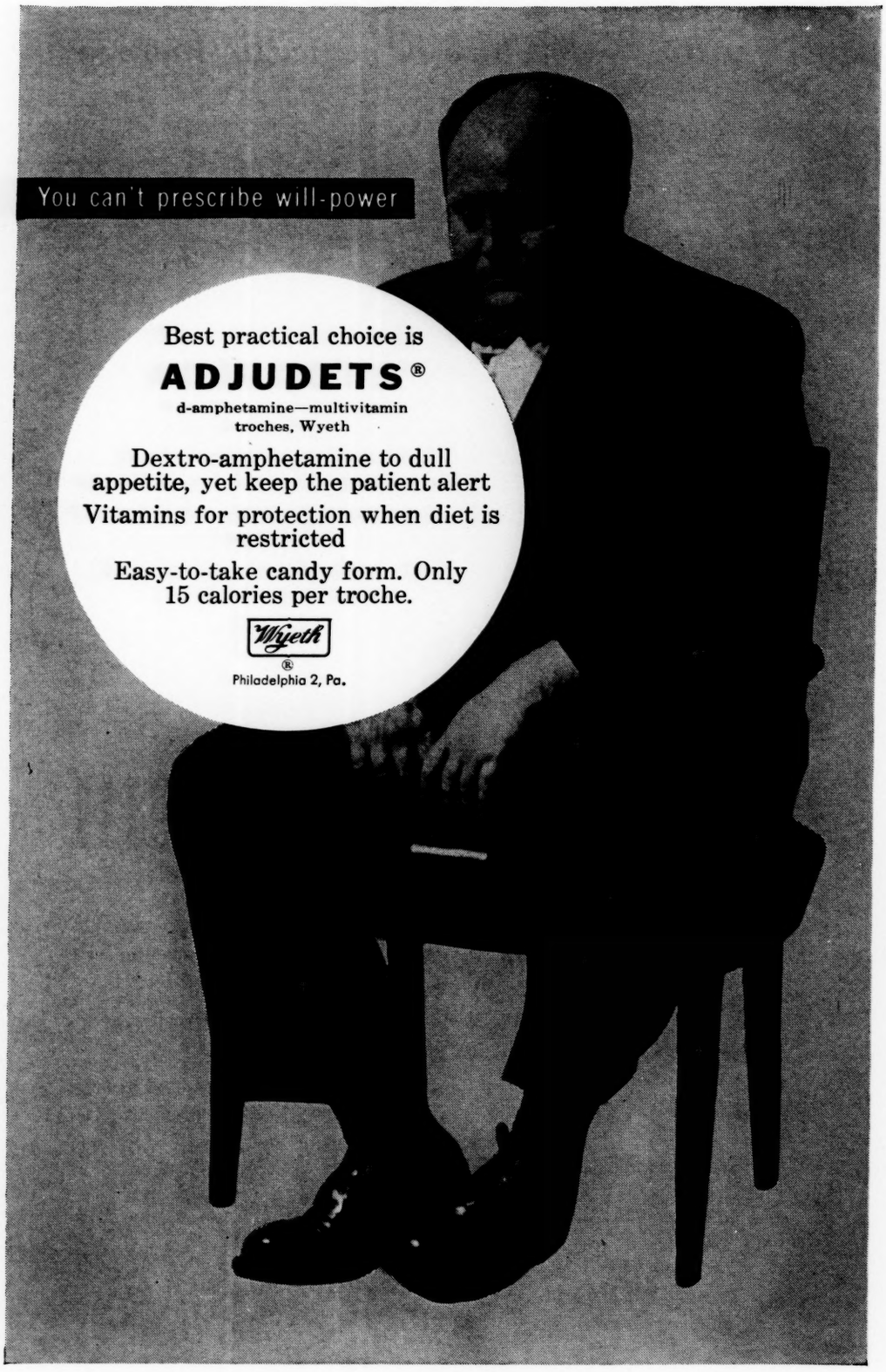
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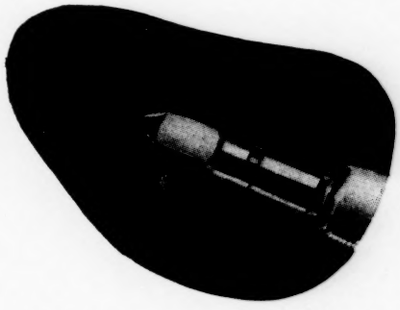

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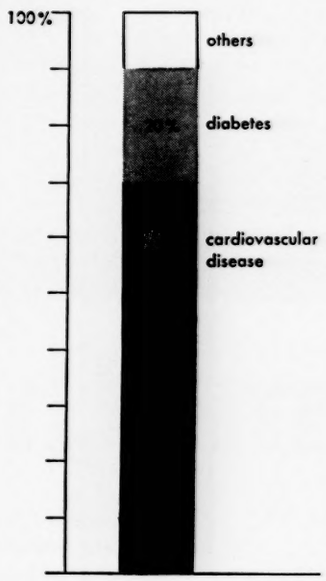

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1. Sherber, D. A., and Levites, M. M.: Hypercholesteremia. Effect on Cholesterol Metabolism of a Polysorbate 80-Choline-Inositol Complex (MONICHOL) J.A.M.A. Vol. 152:682 (June 20) 1953.
2. Keys, A.: J.A.M.A. 147:1514 (Dec. 15) 1951.

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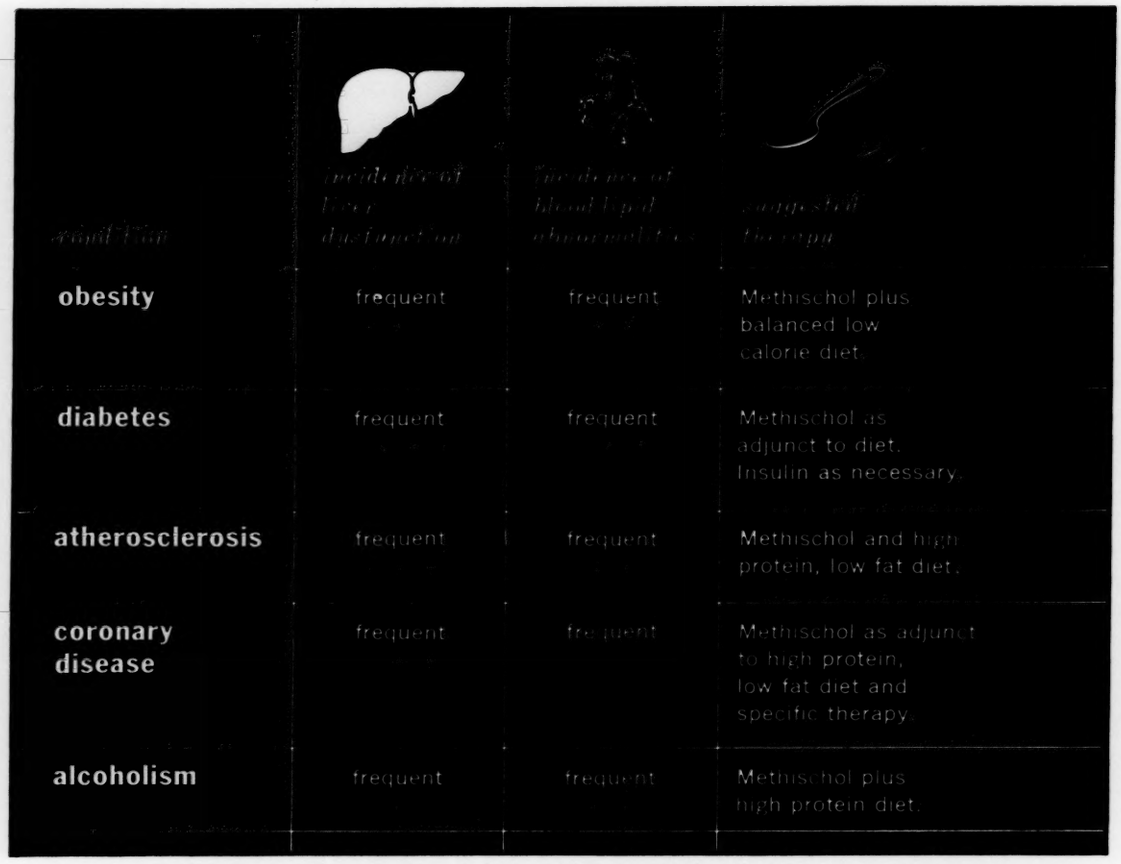

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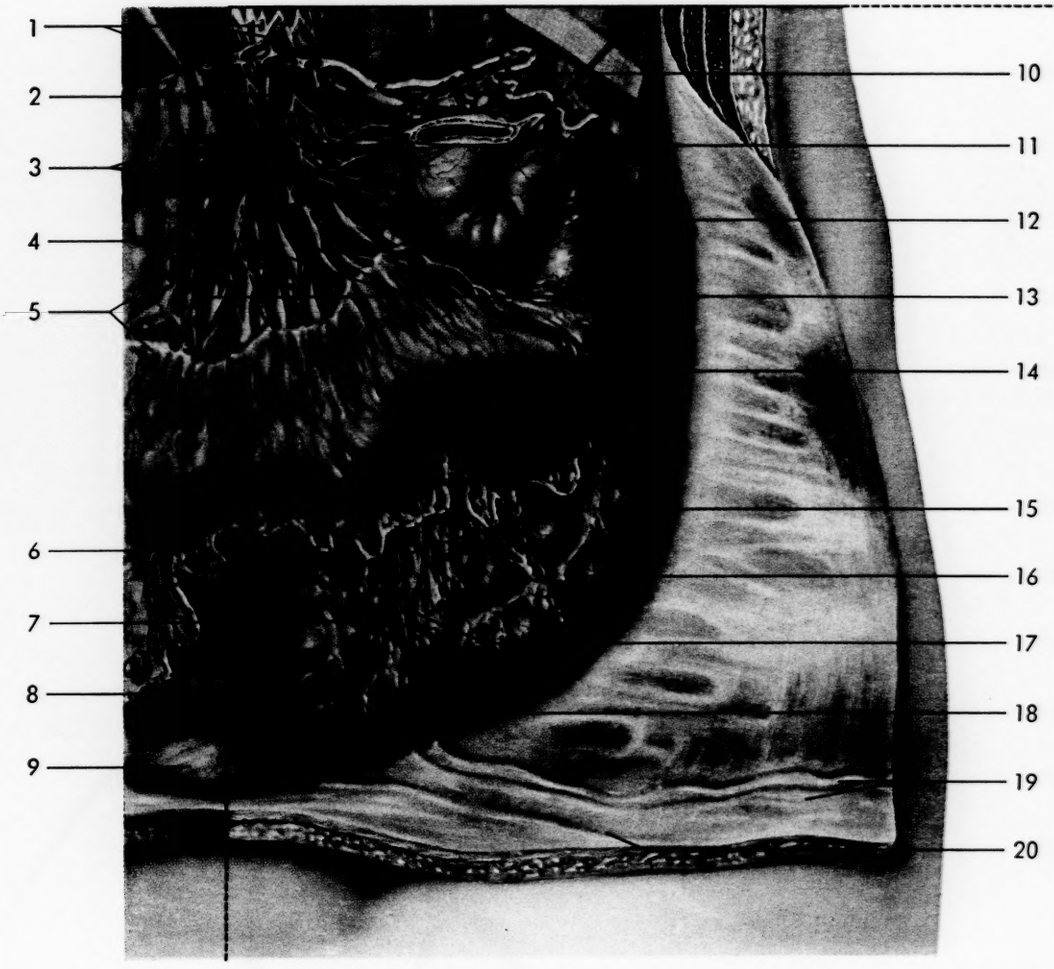

1 Vena cava, aorta and abdominal aortic plexus

2 Branches of superior mesenteric artery and vein

3 Ileocolic lymph node and ileocolic artery and vein

4 Sympathetic abdominal plexus

5 Mesentery

6 Mesenteric lymph nodes

7 Mesocolic lymph nodes

8 Rectum

9 Urinary bladder

10 Inferior mesenteric vein, left colic artery and ureter

11 Intestinal arteries

12 Ileum

13 Intestinal veins

14 Descending colon

15 Branches of sigmoid artery and vein

16 Iliac colon

17 Mesocolon

18 Sigmoid colon

19 Epigastric artery and vein

20 Lateral umbilical ligament

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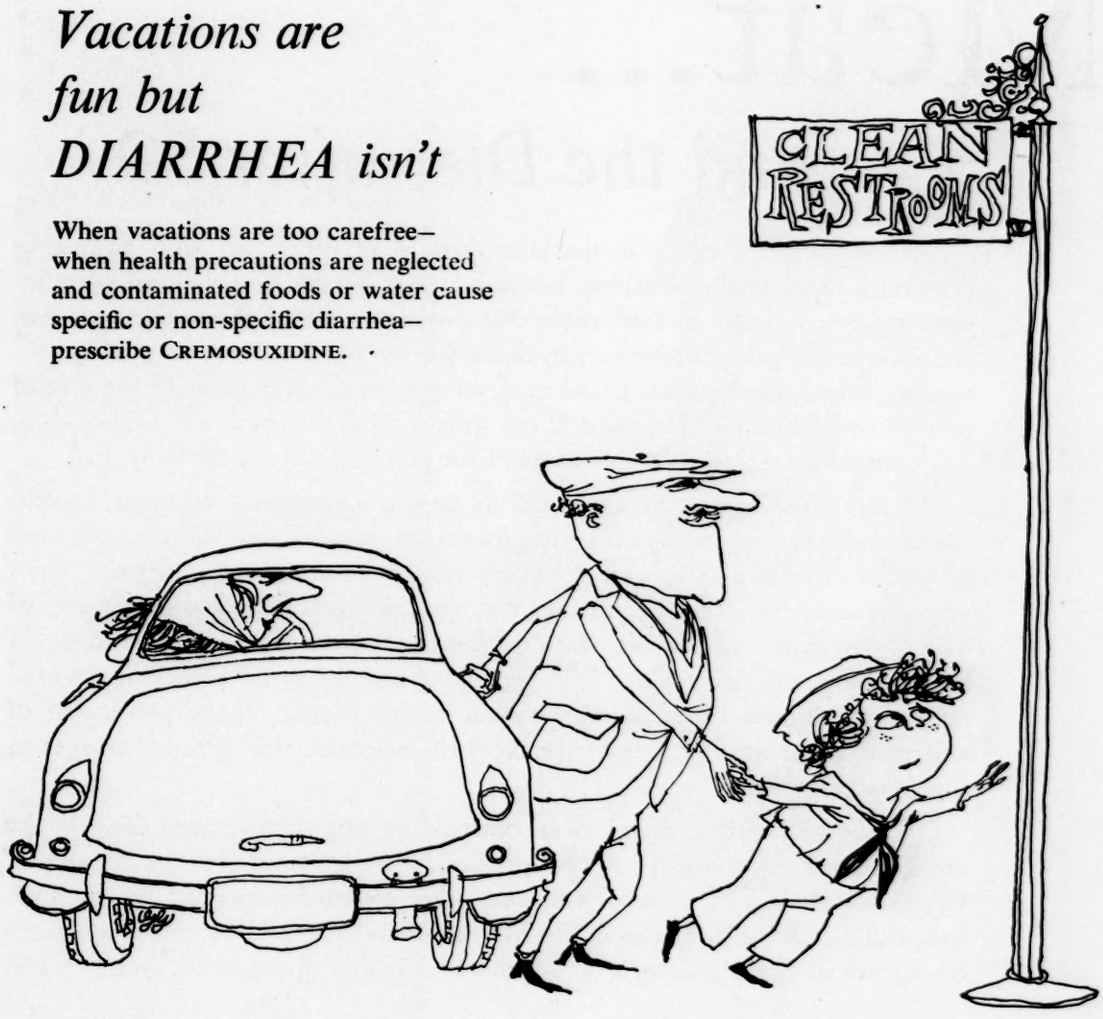

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Meat...

and the Diet after 50

Although caloric needs in the later decades of life lessen with decreasing physical activity and diminishing metabolic rate, clinical observations[1] corroborated by experimental studies[2] show that protein needs of the aging organism continue at the levels of adequacy in earlier years.[3] For avoidance of protein deficiencies, which the aged are prone to develop,[4] the protein quota of the diet of persons over fifty should be more liberal than is often the practice.[5] In providing this quota, lean meat may well be one of the protein foods of the daily diet.

In the years beyond fifty, as well as before, continuous adequate protein nutrition remains an absolute necessity for maintenance of a normal concentration of plasma proteins and, in turn, a normal osmotic pressure of the plasma.[6] Even more pronounced in the aged than in younger persons are the ill consequences of hypoproteinemia—edema, decreased resistance to generalized infection, retarded bone healing, and poor wound healing.[7] Furthermore, dietary protein is essential for the continuous chemical regeneration of cell protein in the prevention of abnormal tissue wasting, one of the most characteristic and obvious changes in the geriatric patient.[8]

But meat is much more than an outstanding protective protein food in the dietary of persons over fifty. It also supplies generous amounts of the B group of vitamins and of iron, phosphorus, and other essential minerals. In the well-balanced diet of the later years of life, meat is just as important for the maintenance of nutritional and physiologic well-being as it is during the earlier years of life.

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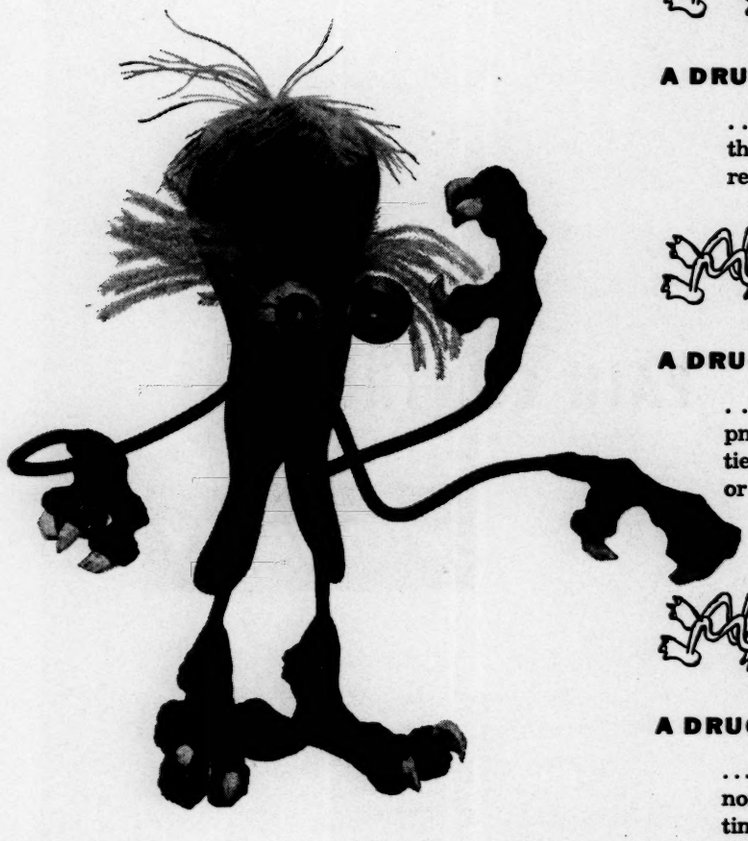

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The American Journal of Medicine

Vol. XV AUGUST, 1953 No. 2

Editorial

Shotgun Antianemic Therapy

An ancient form of antianemic treatment which is still in use today, iron therapy, had its origin in symbolism—the gaining of the strength of steel by drinking the water in which a sword had been dipped. Today symbolism still plays an important role in the selection of antianemic remedies.

Until the turn of the century little was known concerning the pathogenesis of anemia. The need for therapeutic measures existed but there was no foundation of knowledge on which treatment could rest. Today a deficit in oxygen-carrying pigment can be measured with considerable accuracy and different types of anemia can be distinguished.

It has been established without any qualification that iron therapy is effective in the treatment of iron-deficiency anemia and is useful nowhere else except as a prophylactic measure when iron deficiency may develop, as in pregnancy and infancy. It is possible to recognize iron deficiency anemia by simple measures available to all physicians. Furthermore, the administration of iron is easy and the agent is cheap. Salts such as ferrous sulfate and ferrous gluconate are highly effective when given by mouth and usually are well tolerated if properly administered. Only rarely is parenteral iron therapy necessary.

That liver extract therapy is effective only in certain macrocytic anemias such as pernicious anemia, sprue, idiopathic steatorrhea and in related disorders characterized by megaloblastic bone marrow has been proven conclusively. The effect of liver extract appears to be due to its content of vitamin B_{12}, which can be used in place of liver extract. Folic acid can produce a hemopoietic response in pernicious anemia but does not protect the nervous system. Consequently, its use in the treatment of that disease is dangerous. Only in the very rare disorders, "achrestic anemia" and "refractory megaloblastic anemia," and in the uncommon conditions, megaloblastic anemia of infancy and "pernicious anemia of pregnancy," as well as in some cases of sprue, idiopathic steatorrhea and nutritional macrocytic anemia does folic acid have a place in the treatment of anemia. Of the megaloblastic macrocytic anemias encountered in the United States those requiring vitamin B_{12} are far more common than those in which folic acid is needed. Since folic acid is contraindicated in pernicious anemia and since this is by far the most common cause of megaloblastic macrocytic anemia in this country the use of mixtures of vitamin B_{12} and folic acid is unwise.

In no other forms of anemia than those just mentioned is there any justification for the use of liver extract, vitamin B_{12} or folic acid. None of these substances has any influence on the anemia associated with infection or that accompanying malignant disease, renal disease or leukemia. Iron also has no value in these disorders unless they have been complicated by loss of blood of a degree sufficient to produce a deficiency of iron. The anemia in these conditions is affected only by those measures which relieve the underlying disorder. Blood transfusion is useful, of course, but only as a temporary procedure. The therapeutic goal should be to attack the cause of the anemia if that is possible. This comment applies also to the anemia accompanying hypothyroidism and that related to scurvy, both relatively rare conditions.

The use of any of these therapeutic agents is futile in the treatment of hemolytic anemias. On the other hand, the value of splenectomy in the relief of congenital hemolytic anemia is a well established fact. In certain instances of acquired hemolytic anemia splenectomy is also justified. The hormones, ACTH and cortisone, may be helpful in the management of acquired hemolytic anemia. In general they appear to be

of value in the management of the anemias only insofar as they influence the underlying disorder.

There is no evidence that "B vitamins" other than B_{12} and folic acid are of value in the treatment of anemia. Thiamin is only remotely concerned in erythropoiesis and the role of riboflavin is a minor one, even in experimentally produced deficiencies in animals. Experimental niacin deficiency is accompanied by anemia but except in pellagra there is no justification for the administration of niacin in the treatment of anemia in man. To prescribe pyridoxine (vitamin B_6) or calcium pantothenate for the treatment of anemia is to assume that deficiencies exist in humans which diligent search has entirely failed to uncover. Finally, it has not been found that liver extracts or that stomach-liver digests, yeast or other similar products offer anything of value for the treatment of anemia which vitamin B_{12} or folic acid do not furnish.

Nothing is gained by supplementing iron with other minerals. It has yet to be proved that even copper has a place in antianemic therapy in man. The wisdom of using cobalt in the treatment of anemia accompanying infection or in other forms of obscure anemia has still to be demonstrated.

In short, the uses of iron, vitamin B_{12}, folic acid, ascorbic acid and desiccated thyroid are specific and well defined while, on the other hand, no indications have been found for the great variety of other vitamins and minerals which are offered in the widely advertised "shotgun" mixtures. Although certain types of anemia such as aplastic anemia and that accompanying renal disease cannot be treated specifically, it is well established that the specific antianemic substances are of no use in their management.

There is no justification for indiscriminate medication and such a practice is obviously dangerous as well as unsatisfactory. There certainly is no need for symbolism or for mysticism. Yet, under the cover of euphonious names, the sales of these nostrums—the present day successors of the patent medicines of yesterday—total in the millions. It is implied that some mysterious beneficial effect will result from their use and that a subtle, ever present nutritional deficiency will be corrected. The valuable confirmation of the diagnosis which can be derived from the response to the specific therapeutic agent is lost while the cost of antianemic therapy is multiplied ten or twentyfold.

MAXWELL M. WINTROBE, M.D.

Clinical Studies

Transposed Pulmonary Veins*

A Correlation of Clinical and Cardiac Catheterization Data

DAVID C. LEVINSON, M.D., GEORGE C. GRIFFITH, M.D., RICHARD S. COSBY, M.D., WILLARD J. ZINN, M.D., GEORGE JACOBSON, M.D., SIM P. DIMITROFF, M.D. *and* ROBERT W. OBLATH, M.D.

Los Angeles, California

THE purpose of this communication is to correlate the clinical criteria and data obtained by cardiac catheterization in anomalous drainage of one or more pulmonary veins into the right heart. Potentially, this is a type of heart disease which can be corrected surgically.

In presenting patients with this anomaly we are following the subclassification of Brody:[1] (1) patients with partial transposition of the pulmonary veins (four cases); (2) patients with complete transposition of the pulmonary veins (two cases); (3) patients in whom partially transposed pulmonary veins appear as a secondary feature of a more complex lesion (four cases).

The most common anomaly of this type encountered is transposition of a pulmonary vein into the superior vena cava.[1] This is followed closely in frequency by anomalous entrance into the right atrium and into the left innominate vein. Drainage into the coronary sinus, inferior vena cava, azygos vein, left subclavian vein and even into the portal vein is less frequent. The vessels from the right lung are involved twice as frequently as those from the left.

The clinical diagnosis of anomalous pulmonary venous drainage was not possible until the advent of cardiac catheterization and angiocardiography. Without these special technics patients with this anomaly are clinically indistinguishable from those with isolated atrial septal defects or with normal hearts. Recent case reports[2–10] have appeared in which this diagnosis has been made during life by means of cardiac catheterization and/or angiocardiography.

METHOD

Under either local or avertin anesthesia a cardiac catheter was introduced into a branch of the left basilic vein and passed successively with fluoroscopic guidance into the superior vena cava, right atrium, right ventricle and pulmonary artery. In all cases the catheter was also passed directly into one or more pulmonary veins from either the superior vena cava or right atrium. Oxygen samples were obtained and analyzed by the van Slyke method. Pressures were measured by strain gauge. An inlying arterial needle was used to record intra-arterial pressures.

CASE REPORTS

Partial Transposition of the Pulmonary Veins into the "Right Heart"

CASE I. A forty-two year old white woman with known pulmonary tuberculosis was admitted for cardiac catheterization. A heart murmur had been detected first at the age of twelve.

Physical examination revealed a well developed white woman in no distress. The blood pressure was 120/60 mm. Hg. The heart was not enlarged to percussion. The rhythm was regular and the rate was 84. P_2 was accentuated. Grade II systolic murmurs were present at the pulmonic and mitral areas. Roentgenograms of the chest (Fig. 1A) showed prominent pulmonary arteries and borderline right ventricular enlargement. At fluoroscopy increased expansile pulsations of the pulmonary arteries were observed. The

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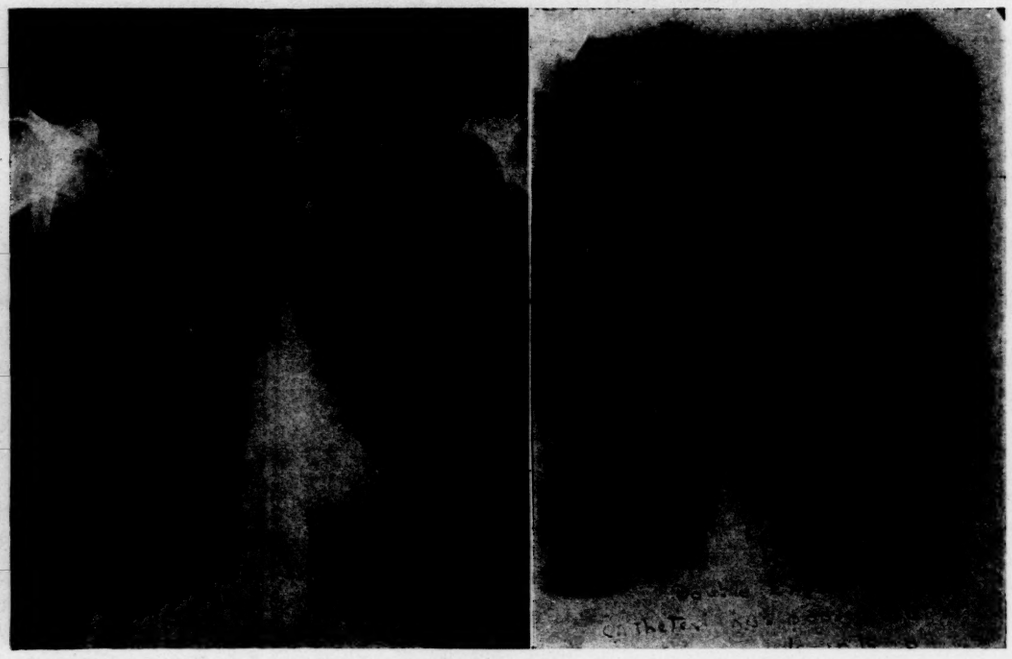
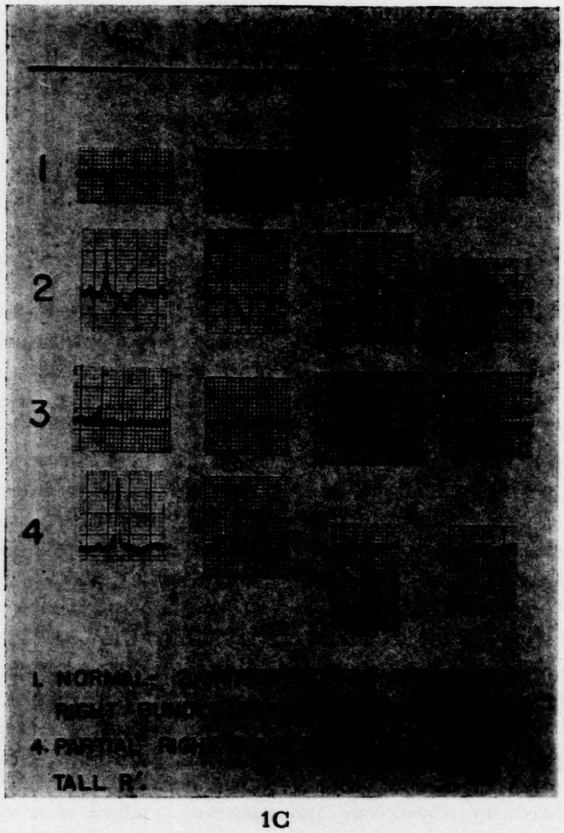


1A 1B



1C

FIG. 1. Case 1. A, chest x-ray; B, catheter in pulmonary vein; C, electrocardiogram.

electrocardiogram (Fig. 1C, No. 3) was that of partial right bundle branch block. The hemoglobin was 12 gm.

Data obtained by cardiac catheterization have been tabulated in Table I. It was possible to pass the catheter from the right atrium directly into a pulmonary vein in the mid-right lung field. (Fig. 1B.) The oxygen saturation of the pulmonary venous blood was found to be 94.7 per cent. The pressure in the pulmonary vein was recorded (Fig. 1D) and the effect of deep inspiration and expiration observed. The pulmonary venous pressure was 12/9 mm. Hg. Inspiration caused an abrupt fall in pressure and expiration a corresponding elevation. A rise in oxygen content of 1.2 volumes per cent occurred between the superior vena cava and right atrium. A slightly elevated pressure (31/21 mm. Hg) was found in the pulmonary artery. An angiocardiogram was done and good visualization of all chambers was obtained. The right atrium and ventricle appeared normal. The main pulmonary artery was moderately enlarged. There was no evidence of early filling of the left atrium or of transposed pulmonary veins.

The diagnosis was made in this instance by passage of the catheter from the right atrium into an anomolous pulmonary vein.

CASE II. A thirteen year old white female was admitted for cardiac catheterization because of a heart murmur first detected at three years of age. Dyspnea occurred on moderate exercise.

Physical examination revealed a well developed young girl. The blood pressure was 120/80 mm. Hg. The heart was not enlarged. A systolic thrill was present at the pulmonic area. The rhythm was regular and the rate was 80. P_2 was accentuated. There was a loud, harsh pulmonic systolic murmur which radiated to the left clavicle. Roentgenograms of the chest (Fig. 2A) showed prominent pulmonary arteries. There was borderline right ventricular enlargement. At fluoroscopy the pulmonary arteries had increased expansile pulsations. The electrocardiogram (Fig. 1C, No. 3) showed partial right bundle branch block. The hemoglobin was 15.5 gm.

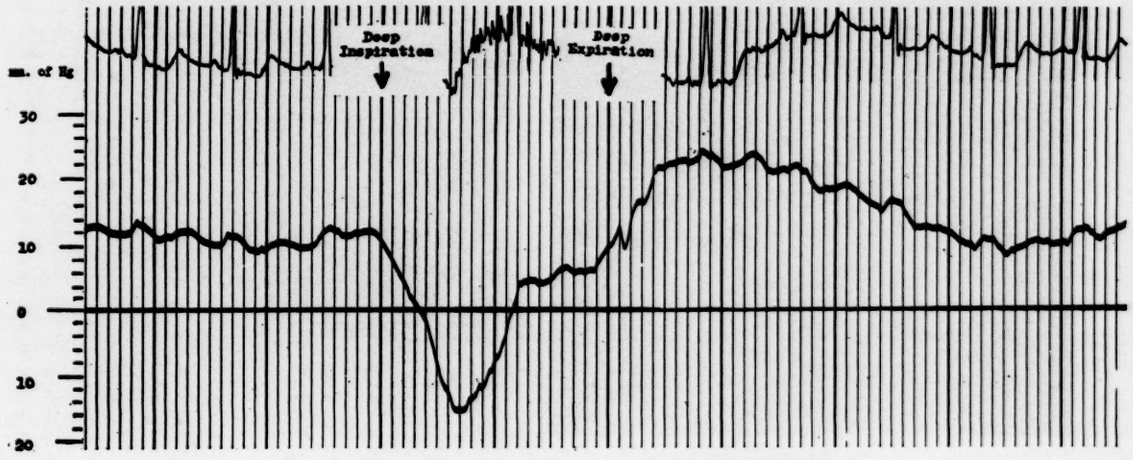
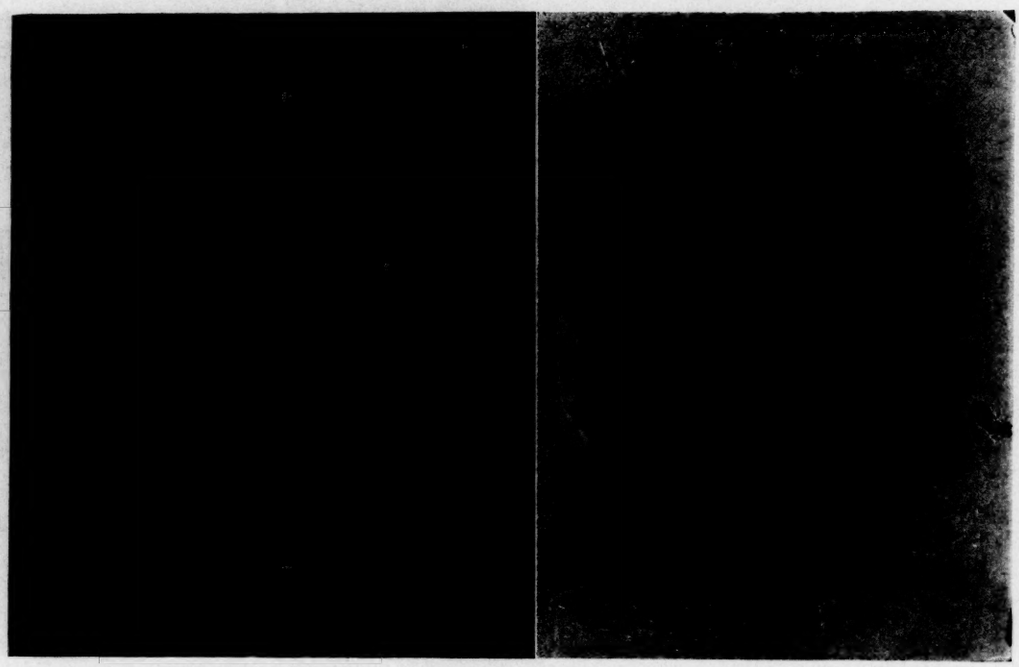


FIG. 1D. Case I. Pulmonary vein pressure study.

TABLE I
FINDINGS AT CARDIAC CATHETERIZATION IN CASE I

Station	Pressure (mm. Hg)		Oxygen Content (Volumes %)	Oxygen Saturation (%)
	Systolic	Diastolic		
Superior vena cava	6	2	11.6	71.8
Right atrium	6	2	12.8	77.7
Right pulmonary vein	12	9	15.7	94.7
Right ventricle	31	0	14.5	88.2
Main pulmonary artery	31	21	14.6	88.4
Left brachial artery	120	60	15.6	94.1

Arbitrary oxygen consumption: 186 cc. per min. Oxygen capacity: 100 per cent saturation, 16.5 volumes per cent. Approximate peripheral blood flow: 4.8 L. per min. Approximate pulmonary blood flow: 18.6 L. per min. Approximate shunt flow: 13.8 L. per min.



2A 2B

FIG. 2. Case II. A, chest x-ray; B, catheter in pulmonary vein.

Data obtained by cardiac catheterization have been tabulated in Table II. The catheter was observed to pass directly from the superior vena cava into two different pulmonary veins in the mid- and upper right lung fields. (Fig. 2B.) The oxygen saturations in the pulmonary veins were 90.3 and 91.9 per cent, respectively. The pulmonary venous pressure was 11/4 mm. Hg. A rise in oxygen content of 1.3 volumes per cent occurred between the superior vena cava and right atrium. A slightly elevated pressure, 31/6 mm. Hg, was present in the pulmonary artery.

TABLE II
FINDINGS AT CARDIAC CATHETERIZATION IN CASE II

Station	Pressure (mm. Hg)		Oxygen Content (Volumes %)	Oxygen Saturation (%)
	Systolic	Diastolic		
Superior vena cava	1	0	12.0	71.0
Right atrium	1	0	13.3	79.1
Right pulmonary vein No. 1	11	4	15.2	90.3
Right pulmonary vein No. 2	11	4	15.5	91.9
Right ventricle	31	0	13.8	82.1
Main pulmonary artery	31	6	13.7	81.3
Peripheral right pulmonary artery	..	..	14.7	87.2

Arbitrary oxygen consumption: 210 cc. per minute. Oxygen capacity: 100 per cent saturation, 16.5 volumes per min. Approximate peripheral blood flow: 6.1 L. per min. Approximate pulmonary blood flow: 12.3 L. per min. Approximate shunt flow: 6.2 L. per min.

The diagnosis in this case was made by passage of the catheter from the superior vena cava into two pulmonary veins.

Partial Transposition of the Pulmonary Veins into the Right Heart with an Atrial Septal Defect

CASE III. A twenty-six year old white woman was admitted for cardiac catheterization. A heart murmur was first detected at five years of age. She complained of palpitation and of a "sighing" type of dyspnea.

Physical examination revealed a well developed young woman. The blood pressure was 115/70 mm. Hg. The heart was not enlarged. The rhythm was regular and the rate was 90. P_2 was equal to A_2. A soft systolic murmur accentuated by exercise was heard at the pulmonic area. Roentgenograms of the chest showed a normal-sized heart with increased prominence of the pulmonary artery segment.

The electrocardiogram showed right axis deviation. The V and A-V leads showed a vertical heart with clockwise rotation. The hemoglobin was 12.8 gm.

Data obtained by cardiac catheterization have been tabulated in Table III. The catheter was observed to pass directly from the right atrium into a pulmonary vein in the right midlung field. The catheter also was passed through an atrial septal defect into the left atrium and from there into a pulmonary vein in the left lung field. The oxygen saturation was 90.3 per cent in the anomalous right pulmonary vein and 97.0 per cent in the left pulmonary vein. The pressure was 7/2 mm. Hg in the right pulmonary vein and 7/3 mm. Hg in the left pulmonary vein. The left peripheral pulmonary vein pressure was 14/7 mm. Hg. A rise in oxygen content of 3.2 volumes per cent occurred between the superior vena cava and the lower portion of the right atrium. A slightly elevated pressure (30/12 mm. Hg) was present in the pulmonary artery.

TABLE III
FINDINGS AT CARDIAC CATHETERIZATION IN CASE III

Station	Pressure (mm. Hg)		Oxygen Content (Volumes %)	Oxygen Saturation (%)
	Systolic	Diastolic		
Superior vena cava	3	1	13.5	77.3
Right atrium (high)	4	1	13.9	79.9
Right atrium (low)	4	1	16.7	95.9
Right pulmonary vein	7	3	15.7	90.3
Left atrium	6	1	....	....
Left pulmonary vein	7	2	16.9	97.0
Peripheral left pulmonary vein	14	7	....	....
Right ventricle (body)	30	0	16.0	91.7
Main pulmonary artery	30	12	14.5	83.0
Left femoral artery	..	..	15.6	89.6

Arbitrary oxygen consumption: 197 cc. per min. Oxygen capacity: 100 per cent saturation, 17.4 volumes per cent. Approximate peripheral blood flow: 7.3 L. per min. Approximate pulmonary blood flow: 11 L. per min.

The diagnosis of an anomalous pulmonary vein was made in this instance by passage of the catheter directly from the right atrium into a pulmonary vein. Passage of the catheter from the right atrium to the left atrium and into a pulmonary vein established the additional presence of an atrial septal defect.

Partial Transposition of the Pulmonary Veins into the Right Heart with an Atrial Septal Defect, Complicated by Congestive Heart Failure

CASE IV. A thirty year old Mexican woman was admitted for cardiac catheterization. Five years prior to entry she noticed the onset of dyspnea and cyanosis upon exertion. Recently digitalis had been prescribed for congestive heart failure. In 1938 she had Raynaud's disease for which sympathectomy was performed in 1947. In 1948 pulmonary tuberculosis was treated successfully with pneumoperitoneum.

Physical examination revealed a thin, small, poorly developed woman in no distress. The blood pressure was 120/80 mm. Hg. The lungs were clear. There was marked cardiac enlargement. The rhythm was regular and the rate was 80. A prominent systolic thrill was felt at the pulmonic area. P_2 was greatly accentuated. Grade III systolic murmurs were present both at the pulmonic and mitral areas. The liver was felt 3 fingers beneath the right costal margin and was very tender. Roentgenograms of the chest showed increased prominence of the pulmonary artery segment. Marked generalized cardiac enlargement was present. The electrocardiogram showed right axis deviation, partial right bundle branch block and right ventricular hypertrophy. The hemoglobin was 13 gm.

Data obtained by cardiac catheterization have been tabulated in Table IV. The catheter was observed to pass directly from the superior vena cava into two different pulmonary veins in the mid- and lower right lung fields. The oxygen saturations in the pulmonary veins were 88.2 and 84.2 per cent, respectively. The pulmonary venous pressure averaged 21/13 mm. Hg. Right heart failure with tricuspid insufficiency was present as evidenced by a pressure of 71/15 mm. Hg in the right ventricle and 15/4 mm. Hg in the right atrium. A rise in oxygen content of only 0.5 volumes per cent occurred between the superior vena cava and right atrium. The oxygen content in the femoral artery was 80 per cent as compared to 88.2 and 84.2 per cent in the pulmonary veins. Whether arterial desaturation was due to a primary pulmonary factor (desaturation of pulmonary vein blood) or to an atrial septal defect with right-left shunt could not be further clarified.

The diagnosis of transposed pulmonary veins

in this case was made by passage of the catheter directly from the superior vena cava into two pulmonary veins.

Complete Drainage of Pulmonary Veins into the Right Side of the Heart

In order for such patients to survive there must be an accompanying atrial septal defect.

TABLE IV
FINDINGS AT CARDIAC CATHETERIZATION IN CASE IV

Station	Pressure (mm. Hg)		Oxygen Content (Volumes %)	Oxygen Saturation (%)
	Systolic	Diastolic		
Superior vena cava	16	4	8.8	46.0
Right atrium (high)	15	4	9.4	50.0
Right atrium (low)	15	4	9.2	49.0
Right pulmonary vein No. 1 (proximal)	20	12	16.6	88.2
Right pulmonary vein No. 1 (peripheral)	24	14	....	....
Right pulmonary vein No. 2	22	14	15.7	84.2
Right ventricle	71	15	9.7	51.2
Main pulmonary artery	70	23	9.3	49.3
Peripheral pulmonary artery	27	14	....	....
Femoral artery	..	..	13.2	80.0

Oxygen consumption: 218 cc. per min. Oxygen capacity: 100 per cent saturation, 18.8 volumes per cent. Approximate pulmonary blood flow: 3.2 L. per min.

This is necessary in order that blood may reach the left atrium and subsequently the systemic circulation. If a patent foramen ovale has acted as a life-saving valve during fetal life, its closure in days or months after birth brings a prompt cessation of life. Survival beyond infancy may result if an atrial septal defect is present or if the atrial septum is absent.

CASE V. A four year old white female was admitted for cardiac catheterization. For the past two years she had had numerous hospitalizations because of recurrent congestive heart failure accompanied by moderate cyanosis. Auricular fibrillation occurred during several admissions.

Physical examination revealed a small white female who was mildly cyanotic. The blood pressure was 100/65 mm. Hg. There was marked cardiac enlargement. The rhythm was irregular and the rate was 70. P_2 was accentuated. At the pulmonary area there was a grade III systolic murmur and at the mitral area there were systolic and mid-diastolic murmurs. Roentgenograms of the chest (Fig. 3A) showed very prominent pulmonary arteries and moderate right ventricular enlargement. The electrocardiogram showed A-V dissociation and right ventricular hypertrophy. (Fig. 1C, No. 4.) The hemoglobin was 15.6 gm.

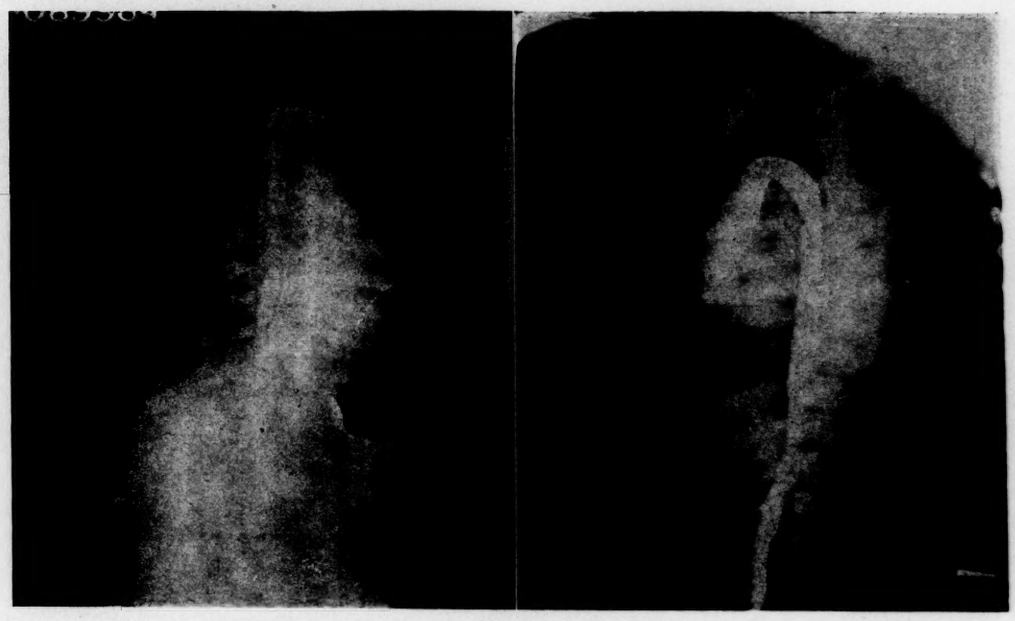
TABLE V
FINDINGS AT CARDIAC CATHETERIZATION IN CASE V

Station	Pressure (mm. Hg)		Oxygen Content (Volumes %)	Oxygen Saturation (%)
	Systolic	Diastolic		
Left innominate vein	..	..	11.3	67.0
Superior vena cava	2	0	13.2	77.3
Right pulmonary vein	11	4	15.0	88.6
Right atrium	2	0	13.5	79.6
Inferior vena cava	1	0	11.8	69.4
Right ventricle	41	0	13.2	77.3
Left pulmonary artery	41	11	13.3	78.5
Probable femoral artery	..	..	12.3	72.7

Arbitrary oxygen consumption: 93 cc. per min. Oxygen capacity: 100 per cent saturation, 21.1 volumes per cent. Approximate peripheral blood flow: 2.0 L. per min. Approximate pulmonary blood flow: 4.0 L. per min. Approximate shunt flow: 1.9 L. per min.

Data obtained by cardiac catheterization have been tabulated in Table v. The catheter was observed to pass directly from the right atrium into a pulmonary vein. The oxygen saturation of the pulmonary venous blood was 88.6 per cent. There was a rise in oxygen content of 3.7 volumes per cent between the left innominate vein and the right atrium. The pulmonary venous pressure was 11/4 mm. Hg. The pulmonary artery pressure was elevated (41/11 mm. Hg).

The diagnosis was made by passage of the catheter from the right atrium into an anomalous pulmonary vein. An angiocardiogram was done in the right posterior oblique position with Neo-iopax injected into the left femoral vein. The inferior vena cava (Fig. 3B) was found to have an anomalous course. Its path was upward along the posterior mediastinum and then sharply curved forward to insert into the



3A 3B

FIG. 3. Case V. A, chest x-ray; B, angiocardiogram demonstrating anomalous inferior vena cava.

superior portion of the right atrium. The hepatic veins emptied directly into the right atrium. The right atrium and ventricle were only diffusely outlined so that no conclusion could be drawn as to their actual size.

Surgical exploration was performed May 16, 1950, at the Harbor General Hospital. Complete transposition of the pulmonary veins into the right atrium and the superior vena cava was found. The main trunk of the left pulmonary veins was anastomosed to the left auricular appendage. Recovery from surgery was uneventful and since surgery the patient has shown definite improvement.

CASE VI. A twenty-five year old white woman was admitted for cardiac catheterization. A heart murmur was first heard nine years previously. For the past three years the patient had had increasing dyspnea on mild exertion.

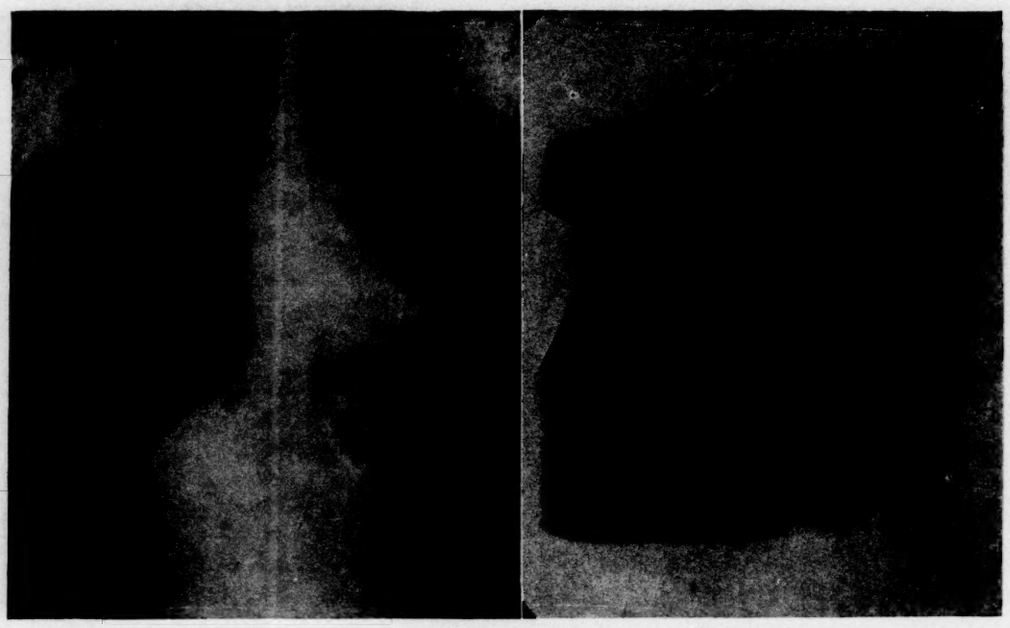
Physical examination revealed a thin, poorly developed white woman. The blood pressure was 90/70 mm. Hg. The heart was moderately enlarged. The rhythm was regular and the rate 80. P_2 was accentuated. At the mitral area there was a grade II systolic murmur and at the pulmonic area a grade IV systolic murmur and a grade III diastolic murmur. Roentgenograms of the chest (Fig. 4A) showed moderate right ventricular enlargement and increased prominence of the pulmonary artery segment. Increased expansile pulsation of the pulmonary arteries was present at fluoroscopy. The electrocardiogram was that of right ventricular hypertrophy. (Fig. 1C, No. 2.) The hemoglobin was 11.6 gm.

TABLE VI
FINDINGS AT CARDIAC CATHETERIZATION IN CASE VI

Station	Pressure (mm. Hg)		Oxygen Content (Volumes %)	Oxygen Saturation (%)
	Systolic	Diastolic		
Superior vena cava (high)	3	1	13.8	82.3
Superior vena cava (low)	3	1	14.7	88.2
Pulmonary vein No. 1	9	6	15.8	95.1
Right atrium (high)	3	1	14.9	89.5
Right atrium (low)	3	1	14.0	83.4
Pulmonary vein No. 2 (peripheral)	13	6	15.9	95.8
Right ventricle	43	0	14.1	84.0
Main pulmonary artery	43	21	14.1	84.0
Peripheral pulmonary artery	21	11	14.1	84.0
Femoral artery	..	..	15.9	95.8

Oxygen consumption: 145 cc. per min. Oxygen capacity: 100 per cent saturation, 16.7 volumes per cent. Approximate pulmonary blood flow: 8.5 L. per min.

Data obtained by cardiac catheterization have been tabulated in Table VI. The catheter



4A 4B

FIG. 4. Case VI. A, chest x-ray; B, catheter in pulmonary vein.

was observed to pass directly from the superior vena cava and from the right atrium into two different pulmonary veins in the right lung field. (Fig. 4B.) Oxygen saturation of both pulmonary veins was 95.1 and 95.8 per cent. Pulmonary venous pressures were 9/6 and 13/6 mm. Hg. Forced expiration caused a rise, and inspiration a fall in pulmonary venous pressure. The pulmonary artery pressure was elevated (43/21 mm. Hg). The estimated pulmonary blood flow was 8.5 L. per minute. The oxygen saturation of the blood in the superior vena cava was abnormally elevated, because of its pulmonary venous drainage, to 88.2 per cent. Unfortunately no inferior vena cava sample was obtained so that the oxygen content of mixed venous blood was not known. Because of this the peripheral blood flow and shunt flow could not be calculated.

An angiocardiogram was done after completion of the catheterization. The right atrium and right ventricle were well visualized and appeared normal. The main pulmonary artery and its smaller branches were markedly dilated. There was no evidence of early filling of the left atrium or left ventricle, nor were transposed pulmonary veins demonstrated.

Surgical exploration was performed April 2, 1951, at the Harbor General Hospital. Complete transposition of the pulmonary veins was found. One vein from the right lung entered the superior vena cava just above its junction with the right atrium. The pulmonary veins from the left lung appeared to join just before entering the right atrium. The left atrial appendage was anastomosed to the left superior pulmonary vein.

The patient was returned to the ward in good condition but expired suddenly several hours after completion of surgery. Permission for a postmortem examination was not obtained.

Partial Drainage of the Pulmonary Veins into the "Right Heart," Accompanied by Other Anomalies

A. Pulmonic valvular stenosis with partial transposition of the pulmonary veins and intact ventricular septum. (We were unable to find a similar case in the literature studied by cardiac catheterization and confirmed by surgical exploration.) This case presented two separate surgically correctable anomalies.

CASE VII. An eleven year old white male was admitted for cardiac catheterization. Cyanosis on exertion had been present since birth. Activity was limited because of dyspnea on exertion.

Physical examination revealed a poorly developed eleven year old boy with a pigeon-type chest deformity. The blood pressure was 105/75 mm. Hg. The heart was slightly enlarged. A

systolic thrill over the left precordium was most prominent at the second and third left interspaces adjacent to the sternum. The rhythm was regular and the rate was 90. P_2 was diminished. There was a grade IV harsh systolic murmur best heard at the second and third left interspaces which was transmitted to both axillas, to the back and into the neck. Roentgenograms of the chest were normal. The electrocardiogram was that of right ventricular hypertrophy. (Fig. 1C. No. 2.) The hemoglobin was 13.5 gm.

Data obtained by cardiac catheterization have been tabulated in Table VII. The catheter was observed to pass directly from the right atrium into a pulmonary vein in the right lung field. The oxygen saturation in the pulmonary vein was 93.8 per cent. The pulmonary venous pressure was 11/7 mm. Hg. The effect of respiration on pulmonary venous pressure is illustrated in Figure 5, expiration causing a rise and inspiration a fall. Finally the catheter was passed from the right ventricle through the pulmonary valve into the pulmonary artery. The finding of right ventricular hypertension and pulmonary artery hypotension confirmed the diagnosis of pulmonic stenosis. The abrupt rise in pressure suggested that the stenosis was valvular rather than infundibular.

Surgery was performed on January 29, 1951, at the Harbor General Hospital. The pulmonary veins from the left lung were found to enter the left atrium normally. Through a stab wound in the right ventricle a valvulotome was introduced and passed into the pulmonary artery. Marked stenosis of the pulmonary valve was present. The valve was incised and dilated. The surgical exposure was inadequate to demonstrate the anomalous pulmonary vein.

Recovery from surgery was excellent and the patient has been definitely improved since surgery.

B. Left superior vena cava entering a sinus venosus in common with the hepatic veins, accompanied by partial transposition of the pulmonary veins into the "right heart."

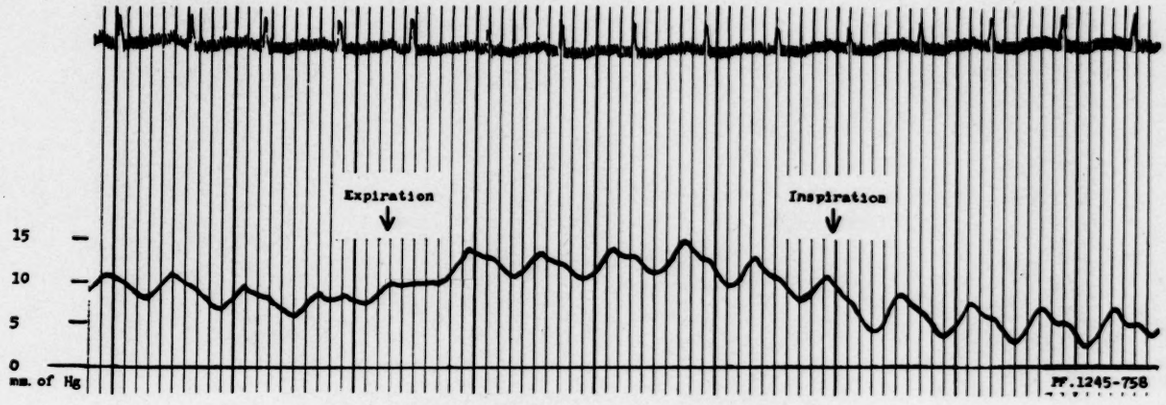


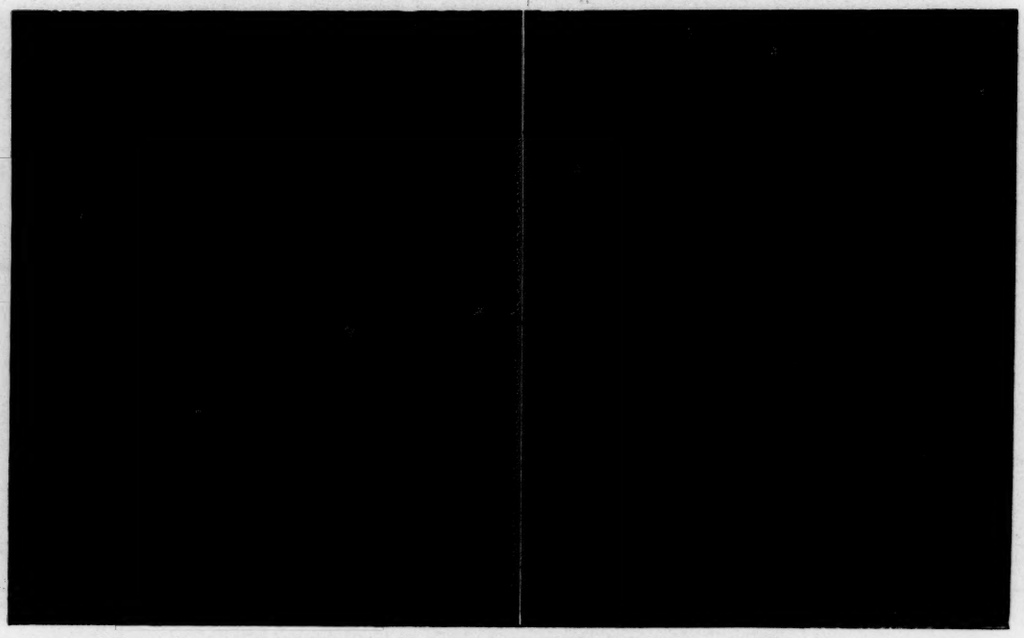
FIG. 5. Case VII. Pressure study in pulmonary vein.

TABLE VII
FINDINGS AT CARDIAC CATHETERIZATION IN CASE VII

Station	Pressure (mm. Hg)		Oxygen Content (Volumes %)	Oxygen Saturation (%)
	Systolic	Diastolic		
Left innominate vein	..	..	14.9	72.5
Superior vena cava	3	1	14.3	69.6
Right pulmonary vein	11	7	19.3	93.8
Right atrium	3	1	16.5	80.1
Right ventricle	135	0	15.6	76.1
Main pulmonary artery	13	8	15.3	74.7
Right femoral artery	..	..	18.6	91.5

Oxygen consumption: 148 cc. per min. Oxygen capacity: 100 per cent saturation, 20.5 volumes per cent. Approximate peripheral blood flow: 2.9 L. per min. Approximate pulmonary blood flow: 3.7 L. per min. Approximate shunt flow: 1.2 L. per min.

CASE VIII. A seven year old white boy was admitted for cardiac catheterization with the history of ready fatigue, dyspnea on slight exertion and intermittent attacks of cyanosis.



6A 6B

FIG. 6. Case VIII. A, chest x-ray; B, angiocardiogram demonstrating a left superior vena cava draining into a ductus venosus communicating with the hepatic vein.

Since six months of age he had had frequent bouts of pneumonia accompanied by asthma.

TABLE VIII
FINDINGS AT CARDIAC CATHETERIZATION IN CASE VIII

Station	Pressure (mm. Hg)		Oxygen Content (Volumes %)	Oxygen Saturation (%)
	Systolic	Diastolic		
Superior vena cava (high)	3	0	11.7	75.1
Superior vena cava (low)	3	0	12.0	76.9
Right atrium (high)	3	0	14.0	89.5
Right atrium (low)	3	0	14.1	90.1
Pulmonary vein	10	3	14.9	95.3
Right ventricle	32	0	13.9	89.0
Main pulmonary artery	32	15	14.0	89.5
Femoral artery	..	..	14.1	90.1

Oxygen consumption: 130 cc. per min. Oxygen capacity: 100 per cent saturation, 15.6 volumes per cent. Approximate peripheral blood flow: 4.0 L. per min. Approximate pulmonary blood flow: 14.4 L. per min. Approximate shunt flow: 10.4 L. per min.

Physical examination revealed a poorly developed white male in no distress. The blood pressure was 90/70 mm. Hg. There was anterior bulging of the sternum and left precordium. There was marked cardiac enlargement, with the point of maximum impulse in the fifth interspace at the anterior axillary line. The rhythm was regular and the rate was 120. P_2 was accentuated. There was a grade III systolic murmur best heard at the pulmonic area which was transmitted upward toward the left clavicle. Roentgenograms of the chest (Fig. 6A) showed increased prominence of the pulmonary arteries. There was moderate cardiac enlargement which appeared to be predominantly in the right ventricle. The electrocardiogram was that of right ventricular hypertrophy. (Fig. 1C, No. 2.) The hemoglobin was 12.5 gm.

Data obtained by cardiac catheterization have been tabulated in Table VIII. The catheter was observed to pass directly from the right atrium into a pulmonary vein in the mid-right lung field. The oxygen saturation in the pulmonary vein was 95.3 per cent. The pulmonary venous pressure was 10/3 mm. Hg. A rise in oxygen content of approximately 2 volumes per cent occurred between the superior vena cava and right atrium. A slightly elevated pressure (32/15 mm. Hg) was present in the pulmonary artery.

An angiocardiogram was done after completion of the catheterization. This demonstrated

(Fig. 6B) a left superior vena cava extending downward along the posterior surface of the heart leading to an extracardiac chamber thought to be the sinus venosus. Numerous hepatic veins communicated with this chamber. The right ventricle was considerably enlarged and the pulmonary artery slightly dilated. There was questionable evidence of an atrial septal defect.

Surgical exploration was performed August 16, 1951, at the Los Angeles County Hospital. Both pulmonary veins from the right lung joined in a common trunk and entered into the right atrium. The right superior vena cava entered the right atrium. The left superior vena cava could not be seen because of the surgical exposure. The anatomic position of the right pulmonary veins was such that the surgeon did not attempt any corrective operation. The chest was closed and the patient returned to the ward in good condition.

C. Tricuspid atresia with partial transposition of the pulmonary veins into the "right heart."

CASE IX. A two year old white male was admitted for cardiac catheterization. Cyanosis on exertion was first observed eight days after birth. Although restricted to a milk diet the patient's growth and development had been normal.

Physical examination revealed a well developed male child in no distress. There was mild cyanosis of the nail beds of both the hands and feet. The blood pressure was 85/50 mm. Hg. The heart was not enlarged. A systolic thrill was present both to the left and right of the sternum in the third and fourth interspaces. The rhythm was regular and the rate 105. A grade IV systolic murmur was present over the entire precordium and was best heard over the area of the thrill. A_2 was greater than P_2. Roentgenograms of the chest showed enlargement of the left ventricle. In the left oblique the right ventricle appeared hypoplastic. The electrocardiogram was that of left ventricular hypertrophy with very tall P waves in leads I and II. The hemoglobin was 13.1 gm.

Data obtained by cardiac catheterization have been tabulated in Table IX. The catheter was observed to pass directly from the right atrium into a pulmonary vein in the mid-right lung field. The catheter was also passed through a very large septal defect into the region of the left atrium. With difficulty the catheter was manipulated into two areas of increased pressure which suggested two different ventricles when the catheter tip position was correlated with the distinctly different pressure curves. The catheter could not be passed into the pulmonary artery. The oxygen saturation in the pulmonary vein was 92.9 per cent. The pulmonary vein pressure was 7/2 mm. Hg. (Fig. 7.) There was a rise in oxygen content of 0.4 volumes per cent between the superior vena cava and the right atrium.

TABLE IX
FINDINGS AT CARDIAC CATHETERIZATION IN CASE IX

Station	Pressure (mm. Hg)		Oxygen Content (Volumes %)	Oxygen Saturation (%)
	Systolic	Diastolic		
Superior vena cava	6	2	9.4	52.6
Right atrium (high)	5	0	9.6	53.7
Right atrium (low)	5	0	9.8	55.3
Right pulmonary vein	7	2	16.5	92.9
Inferior vena cava	..	..	9.5	53.3
Coronary sinus	..	..	5.5	31.0
Right ventricle (?)	20	5	....	....
Left ventricle (?)	55	0	....	....
Femoral artery	..	..	11.5	64.7

Oxygen consumption: 47 cc. per min. Oxygen capacity: 100 per cent saturation, 17.4 volumes per cent. Approximate peripheral blood flow: 2.8 L. per min.

An angiocardiogram was done in the right posterior oblique position with Neo-iopax injected into the left femoral vein. Both the right and left atrium were visualized simultaneously, confirming the impression of a large atrial defect. A small pulmonary artery was visualized. The dye diffused so rapidly that the right and left ventricle could not be identified.

The final diagnosis was that of a transposed pulmonary vein accompanied by a large atrial septal defect with the probable additional anomalies of pulmonary stenosis and tricuspid atresia.

CASE X. A thirteen year old white female with a history of cyanosis since birth was admitted for cardiac catheterization. Dyspnea was present on moderate exertion.

Physical examination revealed a well developed girl who was cyanotic. There was clubbing of both fingers and toes. The blood pressure was 94/80 mm. Hg. There was minimal

cardiac enlargement. The rhythm was regular. There was a grade III systolic murmur which was best heard in the fifth interspace to the left of the sternum. Roentgenograms of the chest showed a prominent left ventricle with a concave pulmonary artery segment. In the left ventricle and from there into the aorta. The catheter could not be passed into the pulmonary artery.

The final diagnosis was that of probable tricuspid atresia, accompanied by an atrial defect, and a transposed pulmonary vein.

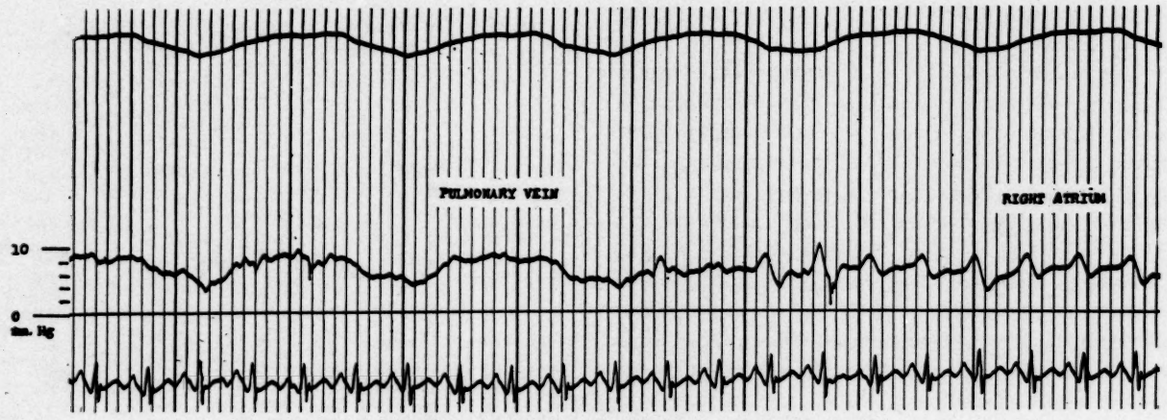


FIG. 7. Case IX. Pulmonary vein and right atrium pressure study.

oblique there was absence of the normal contour of the right ventricle suggesting a small right ventricle. The electrocardiogram showed left axis deviation and probable left ventricular hypertrophy. The hemoglobin was 23.2 gm. and the red blood cell count was 6.4 millions.

TABLE X
FINDINGS AT CARDIAC CATHETERIZATION IN CASE X

Station	Mean Pressure (mm. Hg)	Oxygen Content (Volumes %)	Oxygen Saturation (%)
Superior vena cava	4	14.7	46.8
Right pulmonary vein	5	28.2	90.0
Right ventricle	14	16.8	53.4
Coronary sinus	..	4.5	14.5
Aorta	40	20.4	65.3

Oxygen capacity: 100 per cent saturation, 31.4 volumes per cent.

Data obtained by cardiac catheterization have been tabulated in Table X. The catheter was observed to pass from the right atrium directly into a pulmonary vein in the right lung field. The oxygen saturation of the pulmonary venous blood was 90 per cent. Later the catheter was passed into the coronary sinus and finally through an atrial septal defect into the left

COMMENTS

Data obtained by cardiac catheterization, particularly in Cases I to VI, afford an opportunity to correlate the clinical and cardiac catheterization findings in patients with partial and complete transposition of the pulmonary veins into the right heart.

We are in agreement with Taussig[11] that there are few if any symptoms in patients with partial transposition of pulmonary veins as the sole anomaly (see Cases I and II). One patient had dyspnea on moderate exertion and the other had no limitation of physical activity. The patients with complete transposition (Cases V and VI) had more impressive histories. One had several hospitalizations because of congestive heart failure since early infancy and the other had progressively increasing dyspnea on mild exertion. Growth and development were normal in the patients with partial transposition whereas both patients with complete transposition were small of stature and considerably underweight.

The heart was of normal size in the patients with partial transposition; moderate enlargement existed in those with complete transposition. Pulmonary systolic murmurs were present in all patients, and in one of the cases of complete transposition the diastolic murmur of pulmonic insufficiency was present. The second pulmonic sound was accentuated in all instances.

The electrocardiogram showed right axis deviation with the pattern of incomplete right bundle branch block in the two cases of partial transposition. With complete transposition there again was right axis deviation but accompanied by a very tall R wave in V_1, the pattern of right ventricular hypertrophy.

Roentgenograms of the chest showed increased prominence of the pulmonary artery segment in most instances. At fluoroscopy most of the patients had increased pulsations of the pulmonary arteries. These findings were most evident in the patients with complete transposition. Right ventricular enlargement was minimal in those with uncomplicated partial transpositions and more marked in those with complete transposition. An exception was noticed in Case III in which, because of the right heart failure, the pulmonary blood flow was not increased. In this patient expansile pulsations of the pulmonary arteries were not observed.

Angiocardiography in five of these patients was of no aid in detecting the anomalous pulmonary vein or the presence of an atrial septal defect which must have existed in the patients with complete transposition. In all cases angiocardiography confirmed the presence of pulmonary artery dilatation, which was most marked in the two patients with complete transposition.

Data obtained by cardiac catheterization also could be readily correlated with the degree of anomalous pulmonary venous drainage.

The oxygen difference between the pulmonary veins and the right heart depends upon the number of transposed pulmonary veins. That is, the greater the degree of transposition, the smaller the pulmonary vein-right heart oxygen difference. Also, the greater the number of transposed pulmonary veins, the greater will be the peripheral vein-right heart oxygen difference, and the less will be the intracardiac right and left heart oxygen difference.

The data on oxygen samples in Cases I to VI illustrate two patterns which were found. The first is the pattern of partial transposition (Cases I to IV) in which a moderate rise of oxygen content occurs between the right heart and the pulmonary vein. With complete transposition of the pulmonary veins, the pulmonary vein-right heart oxygen difference was less than with partial transposition. Also, in complete transposition an atrial septal defect must exist so that the left atrium can obtain blood. This results in an almost complete uniformity of blood samples in all cardiac chambers and the peripheral oxygen values approximate those of the intracardiac chambers. Cases V and VI both illustrate these points. In Case V much greater desaturation of returning venous blood was present than in Case VI.

TABLE XI
PRESSURES IN THE PULMONARY VEIN AND RIGHT ATRIUM

Case No.	Pulmonary Vein (mm. Hg)	Right Atrium (mm. Hg)	Pressure Gradient (mm. Hg)
I	12/9	6/2	6/7
II	11/4	1/0	10/4
III	7/3	4/1	3/2
V	11/4	2/0	9/4
VI	9/6	3/1	6/5
VII	11/7	3/1	8/6
VIII	10/3	3/0	7/3
IX	7/2	5/0	2/2
Average	9.5/4.5	3.3/0.6	6.2/3.9

The oxygen data in partial transposition of the pulmonary veins may be simulated exactly by an atrial septal defect. The differential diagnosis depends in one case upon catheterization of the pulmonary veins, and in the other by catheterization of the left atrium. Catheterization of a transposed pulmonary vein is often fortuitous. In this series only veins entering from the right lung could be catheterized. When the diagnosis is suspected, the right or lateral wall of the superior vena cava and right atrium should be explored. Entrance of the catheter into a low pressure radical of the venous system from which completely oxygenated blood is withdrawn is diagnostic of a pulmonary vein.

It is likely that left pulmonary veins entering the right atrium have occasionally been entered but not recognized. These are most difficult to differentiate from atrial septal defects where the catheter passes through the left atrium and thus into a *normal* left pulmonary vein.

Pressure curves in a pulmonary vein are characteristic and are readily influenced by respiration. (Figs. 1D, 5 and 7.) Forced expiration results in an abrupt elevation in pulmonary venous pressure, and inspiration in a prompt decline.

The pulmonary venous pressure, right atrium pressure and the pressure gradient between these two stations are recorded in Table XI. The presence of a pulmonary vein-atrium pressure

gradient has been previously demonstrated[11,12] in patients with atrial septal defects and/or anomalous pulmonary veins. In our laboratory the average pulmonary vein pressure was 9.5/4.5 mm. Hg and the average atrial pressure 3.3/0.6 mm. Hg. The average pressure gradient between these two stations was 6.2/3.9 mm. Hg. The pressure values in Case IV have not been included because of congestive heart failure, and those of Case X because mean pressures were recorded. Figure 7 demonstrates the pulmonary vein-atrium pressure gradient and the difference in pressure contour between the two stations.

Pulmonary artery pressure studies established slight hypertension in the patients with partial transposition and moderate pulmonary hypertension accompanying complete transposition. Actually, it was observed that the pulmonary artery pressures were unusually low in relation to the size of the pulmonary artery and the frequency of increased expansile pulsations. An exception to these findings was observed in Case IV. In this instance there was an additional complication of congestive heart failure with marked tricuspid insufficiency. This resulted in further elevation of both pulmonary artery and pulmonary venous pressure.

Because of failure to obtain samples of mixed systemic venous blood uninfluenced by pulmonary venous drainage, calculations of cardiac output and pulmonary blood flow could only be estimated in some of our cases. The pulmonary blood flow was reduced in Case IV because of the congestive heart failure and the tricuspid insufficiency.

Finally there is the question of surgical exploration and correction of the anomalous venous drainage. In this series two patients with complete transposition of the pulmonary veins were explored. In both a left pulmonary vein was anastomosed to the left atrial appendage. In one instance this resulted in definite improvement; in the other the patient died a short time after the operation. It is believed that surgery is best reserved for those patients with complete transposition accompanied by increasing limitation of physical activity. Usually surgery is not indicated in patients with partial transposition.

SUMMARY

Ten patients with transposed pulmonary veins are described. These include four patients with partial and two with complete pulmonary vein transposition, in whom cardiac catheterization and clinical findings are correlated. The other patients presented (1) pulmonary valvular stenosis accompanied by partial pulmonary vein transposition, (2) a left superior vena cava entering a sinus venosus in common with the hepatic veins, accompanied by anomalous drainage of the right pulmonary veins into the right atrium, and (3) probable tricuspid atresia with partial pulmonary vein transposition (two cases).

The diagnosis of anomalous pulmonary vein drainage in these cases was made at cardiac catheterization by roentgen visualization of the catheter in the anomalous vein, by a characteristic pulmonary vein pressure curve and finally by 90 to 95 per cent oxygen saturation in the blood sample from the anomalous vein.

Surgical exploration and attempts to correct this anomaly should be reserved for those patients with complete transposition in whom limitation of physical activity is progressive.

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The Diagnosis of Overriding Aorta*

With Special Reference to Circulation Time Tests

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THE diagnosis of overriding of the aorta may be difficult or impossible to establish by methods currently in use. This is not only a problem of academic interest but is important also in evaluating the suitability of patients for operation.[1] The only direct and unequivocal proof of overriding aorta consists of the passage of a cardiac catheter directly into the aorta from the right ventricle. Indirect methods may be divided into those involving pressure relationships among the right ventricle, aorta and peripheral arteries; and those which depend upon the identification, in the aorta or peripheral circulation, of certain tracer substances which have traversed the right ventricle but have not passed through the lungs. These tracer substances include radio-opaque compounds used in angiocardiography, dyes, radioactive substances and other agents ordinarily used in determining the speed of the circulation, and oxyhemoglobin which, by its content of oxygen, may suggest the path it has taken through the body.

It is the purpose of this paper to discuss these methods for diagnosing overriding aorta and to evaluate a test recently developed in our laboratory, in which Evans blue dye is injected directly into the right ventricle through a cardiac catheter and its arrival in the blood vessels of the ear timed by an oximeter. In addition, it will be shown from a review of the literature that the presence of a right aortic arch in a cyanotic patient with congenital heart disease has important implications regarding the diagnosis of overriding aorta.

"Overriding aorta" (or "riding aorta") is an anatomic term which indicates that the vessel, at its origin, straddles the interventricular septum and therefore accepts blood from both ventricles. A high interventricular septal defect must coexist. In the past the words "dextroposition" and "overriding" have been used more or less synonymously to indicate that the aorta receives part of its blood from the right ventricle. Because "dextroposition" may easily be misinterpreted to mean that the aorta lies in relation to the root of the right lung (right-sided aorta) we prefer the term "overriding."

All degrees of overriding may occur and it may be impossible to determine, either clinically or at the autopsy table, how much blood flow each ventricle contributes to the aorta. Furthermore, the amount of blood reaching the aorta from each ventricle may vary in the same patient under different conditions. Because there is no reliable way of establishing the exact anatomic position of the aorta during life, an erroneous diagnosis of overriding aorta may occasionally be made on the basis of physiologic criteria. An example would be a heart with an interventricular septal defect in which the aorta is in its normal position but nevertheless receives a significant portion of right ventricular output.[2]

It will be pointed out that the group of syndromes characterized by central cyanosis due to overriding aorta may usually be distinguished, by special studies, from instances of cyanosis caused by (1) pulmonary stenosis with interatrial septal defect and right to left shunt; (2) interatrial septal defect with pulmonary hypertension and right to left shunt; (3) patent ductus arteriosus with reversed shunt; and (4) primary pulmonary hypertension.

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CURRENT METHODS OF DIAGNOSING OVERRIDING AORTA

For the following discussion the methods in use at the present time for the diagnosis of overriding aorta may best be divided into the following categories: (1) those involving x-rays, including angiocardiography; (2) studies of the speed of the circulation; (3) methods which depend upon the relative saturation of arterial blood with oxygen; and (4) cardiac catheterization studies.

X-ray Methods. Conventional roentgenograms and fluoroscopy of the heart may be dismissed as inadequate.

Angiocardiography. The anatomic position of the opacified aorta relative to the two ventricles may suggest that the aorta arises in whole or in part from the right ventricle. However, it is unusual for the root of the aorta to stand out clearly in angiocardiograms. Furthermore, the most proximal portion of the aorta frequently curves sharply toward the right as it ascends, giving a deceptive picture. For these reasons we do not consider this a reliable criterion.

Premature visualization of the aorta in the course of angiocardiography may suggest overriding.[3] However, this may also occur in several other conditions in which the aorta receives its blood exclusively from the left ventricle, namely:

1. Pulmonary stenosis with interatrial septal defect and reversed shunt. One such case was reported by Sussman et al.[4] and another by Allanby and Campbell[5] (Case 4). Both were proven by postmortem examination. The case which is reported at the end of this paper is another example of this syndrome in which there was early visualization of the aorta in the angiocardiogram without overriding.

Careful examination of angiocardiograms in this disease will usually disclose opaque substance in the left atrium prior to or simultaneous with opacification of the aorta. It has been our experience that the left ventricle may not be opacified at such times despite the fact that diodrast®-containing blood has already passed through that chamber in substantial quantities. The diagnosis of overriding cannot therefore be made if the left atrium is opacified. Premature visualization of the aorta with no evidence of left atrial opacification is, however, good evidence of the presence of overriding.

2. Patent ductus arteriosus with pulmonary hypertension and reversed shunt is the second condition which may lead to premature visualization of the aorta. Although this is rare, two well documented cases have recently been reported.[6,7] The diagnosis may be suspected when the descending but not the ascending aorta is opacified in the early films.

3. On theoretical grounds, three other lesions might lead to premature visualization of the aorta in the angiocardiograms in the absence of anatomic overriding of the aorta, namely, interatrial and interventricular septal defect with pulmonary hypertension and right to left shunt; and tricuspid atresia. The latter malformation is often suggested by conventional roentgenograms and electrocardiography, and is usually diagnosed without difficulty by angiocardiography, cardiac catheterization or both.[8]

Circulation Times. Overriding of the aorta may be suggested by one or more of the following: (1) Shortening of the circulation time from the antecubital vein to the periphery, for example, tongue (saccharin), lips (fluorescein), ear (Evans blue dye); (2) the sensation of tingling in the face or extremities when an ether circulation time is performed;[9] (3) in the presence of a prolonged arm-to-tongue time, such as may occur in congestive heart failure, overriding of the aorta may nevertheless be suspected when the arm-to-lung time (ether) is approximately the same.

Although information obtained by studies of the speed of the circulation may suggest overriding of the aorta, negative results are of little significance. Prinzmetal[10] has emphasized that both the size of the right to left shunt and the concentration of the test substance must be taken into consideration. Only about one-half of the patients in Möller's series[11] of cases of tetralogy of Fallot had shortened "fluorescein times."

It must be apparent that shortening of the circulation time by one of the methods outlined above indicates only that there is a right to left shunt of the test substance in sufficient amount to be detected at the periphery. The site of this shunt, however, cannot be determined in this way. Many of the same comments apply here as to circulation of diodrast during angiocardiography.

We shall demonstrate later in this report that in a case of pulmonary stenosis with interatrial septal defect in which the aorta visualized early during angiocardiography, circulation studies

with ether and calcium gluconate also indicated a large right to left shunt.

Patent ductus arteriosus with reversal of shunt might give rise to similar difficulties in the interpretation of circulation studies, although such studies have not been included in the few instances of this syndrome which have been published. Burchell[12] has pointed out that the course of the circulation in this condition is such that more of the shunted blood reaches the lower than the upper half of the body. This may be reflected in a higher oxygen content of blood in the brachial than the femoral artery.[13] Whether or not sufficient test substance may reach the tongue or ear to give a rapid circulation time is problematic. It is possible that ether injected intravenously might produce tingling in the toes but not in the upper part of the body.

Although circulation data in tricuspid atresia are meager, this condition may also lead to a shortened circulation time.[14] On theoretic grounds it should make no difference whether the aorta arises from the left ventricle or a rudimentary right ventricle which receives its blood via an interventricular septal defect. In either event the right to left shunt is through the interatrial septum.

Arterial Oxygen Saturation. In the presence of overriding aorta oxygen saturation of peripheral arterial blood is usually diminished. However, the presence of peripheral arterial unsaturation is not of itself evidence of overriding. Certain additional observations must be made in order to rule out pulmonary factors or a right to left shunt proximal to the aorta. It is necessary to obtain blood from the left ventricle (an unusual event during cardiac catheterization) and this blood must have an appreciably higher oxygen content than that of a peripheral artery. If left ventricular blood is completely saturated with oxygen, pulmonary factors such as respiratory insufficiency and arteriovenous aneurysm of the lung are eliminated. If, however, the oxygen saturation of left ventricular blood is below normal but appreciably higher than that of a peripheral artery then, in addition to overriding aorta, veno-arterial shunting must have occurred, either in the lung itself or through an interatrial septal defect.

The only conditions, other than overriding aorta, which would lead to unsaturated peripheral arterial blood in the presence of a fully saturated left ventricular sample would be patent ductus arteriosus or aortic septal defect with right to left shunt.

Cardiac Catheterization. As mentioned before, the passage of a cardiac catheter directly into the aorta from the right ventricle is undoubtedly the best evidence of overriding of that vessel. It is theoretically possible that an interventricular septal defect without functional or anatomic overriding might lead to confusion if the catheter reached the aorta via the left ventricle. This is unlikely to occur, however, and has not yet been reported. Furthermore, the finding of identical oxygen contents of blood in the aorta and left ventricle would indicate the true condition. Similar considerations apply to the theoretic possibility of passing a catheter through an aortic septal defect.

The presence of identical systolic pressures in the right ventricle and a peripheral artery (the brachial) has been cited as evidence of overriding aorta.[15] This contention has never been fully documented and indeed physiologic considerations cast some doubt upon it. Hamilton and Dow[16] have shown in dogs, and Salans et al.[17] and Schnabel et al.[18] have recently confirmed in human subjects, that a positive systolic pressure gradient occurs as one progresses from the aorta to the peripheral arteries. Furthermore, even if it should be established that the systolic pressures in the right ventricle and a peripheral artery bore a predictable relationship to each other in the presence of an overriding aorta, one could not be certain in a given case that the findings were not coincidental. On the other hand, a marked difference in the systolic pressures in the right ventricle and brachial artery would effectively rule out an overriding aorta.

CIRCULATION TIME FROM VENTRICLE TO EAR

The shortcomings of the customary methods of determination of the "circulation time" when used for the purpose of identifying an overriding aorta have already been discussed. It has been pointed out that the test substance may appear in the systemic circulation very rapidly and in substantial quantities when veno-arterial shunting occurs through a defect other than an overriding aorta. On the other hand, it has been reported that it may be impossible to demonstrate an abnormally rapid circulation time in the presence of an overriding aorta. The first difficulty is due to the fact that the test substance is injected into the peripheral venous

system and must pass through the right atrium where a shunt of blood into the left atrium may exist. This condition may be encountered in patients who have pulmonary stenosis and an interatrial septal defect.

The second difficulty is due to the fact that a test in which the end point depends upon a subjective response (saccharin, decholin,® ether, etc.) does not measure the time of arrival of the most rapidly moving particles because a certain unknown concentration must be reached before subjective response is evoked. Moreover, variations in the volume of blood contained in the system between the point of injection and the detection point will alter the circulation time. The greater the volume, the slower the time.

A modification of this technic was therefore devised by one of us (R. P. L.) to overcome these difficulties. Technical details are included in a previous publication.[19] The test is performed during the course of the routine diagnostic cardiac catheterization. The test substance (3 to 5 cc. of a 0.5 per cent solution of Evans blue* (T 1824)) is injected directly into the right ventricle through the cardiac catheter and its arrival in the blood vessels of the ear is timed by means of a Millikan oximeter. Pressure tracings are taken before and after the test to confirm the location of the catheter tip. Three cc. of the dye solution are used in small children and 5 cc. in larger children and adults. A stopwatch is begun at the start of the injection and stopped at the first perceptible deflection of the oximeter galvanometer.

Ziegler[20] has independently reported a similar technic using fluorescein as the test substance.

The possibility of veno-arterial shunting through an interatrial septal defect is eliminated by injecting the dye directly into the right ventricle. In addition, because of the high concentration of dye which reaches the ear, its arrival there is signalled instantaneously by the oximeter and there is less possibility of a false negative result. There are, however, two important factors which may affect the circulation time. The right to left shunt may be so small, even in the presence of overriding aorta, that insufficient dye reaches the aorta to give an end point. Furthermore, the site of injection of the dye within the right ventricle must be considered, and may be of increasing importance when one deals with minimal degrees of overriding. In such cases the dye may be injected into a stream of blood going directly toward the pulmonary artery and a long circulation time may be obtained. In order to minimize this possibility we have recently adopted the procedure of placing the catheter tip only a short distance beyond the tricuspid valve prior to injecting the Evans blue.

This test has been performed in forty-four patients who were catheterized for various reasons. Four of these are omitted from discussion because the diagnosis remains in doubt. In the remaining forty patients (Table 1) the diagnosis seems reasonably well established on the basis of clinical, fluoroscopic, electrocardiographic and cardiac catheterization studies. Many of these patients also had angiocardiography. It must be emphasized, however, that without postmortem examination we consider the diagnoses in cases of congenital heart disease as unproved.

The series included one Negro of moderately dark pigmentation, in whom a satisfactory endpoint was obtained.

Overriding aorta was believed to be present in thirteen cases. In Cases 7 and 11 the diagnosis was confirmed by autopsy. In Case 10 the catheter passed into the aorta from the right ventricle. In Case 2, a child with Eisenmenger's complex and an interatrial septal defect, the blood obtained from the left ventricle showed a much greater oxygen content than that of the femoral artery. Thus it could be inferred that there was a shunt of poorly oxygenated blood into the systemic circulation distal to the left ventricle, namely, through an overriding aorta. The presence of overriding aorta was unproved in the remaining nine instances.

The range of circulation times from the right ventricle to the ear in this group of thirteen patients was 3.2 to 13.4 seconds. The circulation time was greater than 5 seconds in only two Cases (Nos. 10 and 11). These patients were unusual in that the right to left shunt at rest was minimal in both, the arterial oxygen saturation amounting to 92.4 per cent in the first and 94 per cent in the second.

In two patients with tricuspid atresia the test was performed from the left ventricle, with rapid circulation times in both (3.8 and 4.2 seconds).

The remaining twenty-five patients in this study were a heterogeneous group whose only common feature was the absence of overriding

* Supplied by the William R. Warner Co., New York, N. Y.

TABLE 1

DATA OF CIRCULATION TIME FROM VENTRICLE TO EAR

Cases with Overriding Aorta

Case No.	Pt.	Age (yr.)	Diagnosis	Circulation Time (sec.)
1.	M. D.	3½	Tetralogy of Fallot	4.7
2.	J. G.	5	Eisenmenger's complex with patent foramen ovale	3.5
3.	S. B.	8½	Tetralogy of Fallot	4.4
4.	G. L.	6	Tetralogy of Fallot	3.5
5.	A. M.	2½	Tetralogy of Fallot	4.0
6.	M. H.	4½	Tetralogy of Fallot	3.2
7.	D. K.	2½	Tetralogy of Fallot with patent foramen ovale	3.3
8.	J. S.	2½	Tetralogy of Fallot	4.0
9.	J. C.	3	Tetralogy of Fallot with patent foramen ovale	3.5
10.	M. S.	32	Tetralogy of Fallot	13.4
11.	G. H.	3½	Tetralogy of Fallot	7.8
12.	J. C.	8	Tetralogy of Fallot with patent foramen ovale	3.8
13.	M. R.	2	Tetralogy of Fallot with patent foramen ovale	3.3

Cases without Overriding Aorta

14.	L. C.	19	Uncomplicated pulmonary stenosis	9.5
15.	M. A.	11	Pulmonary stenosis with interatrial septal defect	7.0
16.	V. D.	32	Pulmonary stenosis with interatrial septal defect	9.5
17.	S. L.	19	Uncomplicated pulmonary stenosis	5.5
18.	E. G.	6½	Patent ductus arteriosus	8.0
19.	M. H.	8	Subaortic stenosis	7.0
20.	C. R.	3	Lutembacher's syndrome	5.3
21.	C. B.	11	Patent ductus arteriosus	6.0
22.	M. D.	32	Pulmonary stenosis with interatrial septal defect	6.0
23.	Y. K.	13	Idiopathic dilatation of the pulmonary artery	7.0
24.	S. D.	6	Pulmonary stenosis with interatrial septal defect	9.0
25.	E. W.	49	Tumor of thymus; normal heart	10.0
26.	R. P.	12	Idiopathic dilatation of the pulmonary artery	7.0
27.	L. C.	27	Interatrial septal defect	8.6
28.	S. J.	6	Normal heart	5.0
29.	L. M.	10	Uncomplicated pulmonary stenosis	6.0
30.	H. M.	48	Pulmonary fibrosis; normal heart	7.6
31.	N. D.	6	Uncomplicated pulmonary stenosis	7.2
32.	G. G.	41	Normal heart (Negro)	8.0

TABLE 1 (*Continued*)

Case No.	Pt.	Age (yr.)	Diagnosis	Circulation Time (sec.)
33.	N. R.	4½	Pulmonary stenosis with interatrial septal defect	7.0
34.	B. S.	35	Interatrial septal defect	11.5
35.	A. R.	21	Interatrial septal defect	8.0
36.	J. C.	6	Normal heart	6.5
37.	L. L.	11	Pulmonary stenosis with interatrial septal defect	10.1
38.	L. S.	6	Uncomplicated pulmonary stenosis	5.6

Dye Injected into Left Ventricle

39.	I. W.	3½	Tricuspid atresia	3.8
40.	J. G.	4½	Tricuspid atresia	4.2

of the aorta. This group included five individuals with normal hearts. The remainder had various forms of congenital heart disease. The circulation times in this group varied from five to eleven and one-half seconds.

Thus in the absence of overriding aorta the right ventricle to ear circulation time was greater than five seconds in every case. When overriding aorta was present the circulation time was less than five seconds except in the two instances with a minimal right to left shunt.

Though these findings are quite encouraging the test needs further study, especially in regard to establishment of the normal range of values in younger children. This is particularly true because in our series the average age of the cases with overriding aorta was much lower than that of the control group.

From the data at hand, however, it is our opinion that a circulation time from the right ventricle to the ear of less than five seconds is very suggestive of overriding of the aorta, and a time of four seconds or less is almost certain evidence. On the other hand, a circulation time of more than five seconds does not rule out overriding aorta, particularly when the right to left shunt is small.

Ziegler,[20] using fluorescein, believes that four seconds is the critical value. His technic, however, differs slightly from ours in that he fills the catheter with the test substance prior to the definitive injection. When allowance is made

for this variation in technic, his figures agree very closely with ours.

It is apparent from the earlier discussion in this paper that the only conditions which could theoretically give a "false positive" Evan's blue test are patent ductus arteriosus with pulmonary hypertension and right to left shunt and interventricular septal defect in combination with either pulmonary hypertension or pulmonary stenosis. In such instances a right to left shunt through the defect would be observed. Furthermore, in complicated anomalies the catheter occasionally enters a ventricular chamber which cannot be further identified. This type of case might also give an Evans blue circulation time difficult of interpretation. The two patients with tricuspid atresia upon whom this test was performed are cases in point. Here, however, it was fairly clear that the dye was injected into the *left* ventricle.

In the performance of the right ventricle to ear circulation time as here depicted further information could probably be obtained by use of a recording type of oximeter[21] which would give the dye concentration in the ear as a function of time.

DIAGNOSTIC VALUE OF RIGHT-SIDED AORTIC ARCH

An abnormal course of the aortic arch may occur as an isolated congenital defect or in association with other anomalies of the heart. Because the presence of right-sided aortic arch may usually be established without difficulty by radiologic means,[22] it is important to determine, if possible, in what conditions it may be found.

Right-sided aortic arch may be associated with other aortic anomalies, such as double aortic arch, persistent left root, unusual origin of the great vessels, etc. Whenever a right aortic arch is present, however, it is usually the main arterial trunk and the other aortic anomalies are of secondary importance anatomically. Therefore, in the succeeding discussion, whenever right-sided aortic arch is mentioned it is

TABLE II

CASES OF RIGHT AORTIC ARCH IN ASSOCIATION WITH OTHER CARDIAC ANOMALIES, PROVEN BY POSTMORTEM EXAMINATION

No.	Author	Age	Sex	Associated Anomalies
1.	Corvisart[27]	3 yr.	?	Tetralogy of Fallot, patent foramen ovale
2.	Peacock[23] (Case 12)	11 mo.	M	Tetralogy of Fallot
3.	Assmann[28]	?	?	Tetralogy of Fallot
4.	Myers[29]	6 yr.	F	Tetralogy of Fallot
5.	Harris and Whitney[30]	19 mo.	?	Aorta and pulmonary artery arise from right ventricle; interventricular septal defect; no pulmonary stenosis; double superior vena cava, the left emptying into coronary sinus; small left aortic arch
6.	Blackhall-Morison[31]	16 mo.	?	Tetralogy of Fallot (pulmonary atresia); patent ductus arteriosus
7.	Wheeler and Abbott[32]	28 yr.	M	Tetralogy of Fallot (pulmonary atresia); persistent left aortic root
8.	Bedford and Parkinson[33] (Case 11)	27 yr.	F	Eisenmenger's complex
9.	Eek, Mannheimer and Sandblom[34] (Case 13)	6 yr.	M	Tetralogy of Fallot; patent foramen ovale
10.	Ibid.[34] (Case 49)	11 yr.	F	Tetralogy of Fallot; interatrial septal defect
11.	Campbell and Hills[3] Case PO23	?	?	Tetralogy of Fallot
12.	Allanby, Brinton, Campbell and Gardner[35] (Case 3)	12 yr.	F	Tetralogy of Fallot (pulmonary atresia); interatrial septal defect
13.	Young and Griswold[36] (Case 1)	23 mo.	F	Levocardia with situs inversus of the abdominal viscera; transposition of the auricles; interventricular septal defect; overriding aorta; patent ductus arteriosus; patent foramen ovale; atresia of the pulmonary orifice
14.	Wittenborg, Neuhauser and Sprunt[8] Wittenborg[37] (one case)	?	?	Tricuspid atresia

understood that other anomalies of the aorta may coexist.

The association of right-sided aortic arch with the tetralogy of Fallot has been known since Corvisart described such a combination in 1806, long before Fallot's contribution to this subject

TABLE III

CARDIAC CATHETERIZATION FINDINGS

Site	Oxygen Content (vol. %)	Per cent Saturation	Pressure (mm. Hg)
Superior vena cava	9.2	40.0	12–5/0–3
Inferior vena cava	13.3	58.6	14–16/4
Right auricle (high)	9.9	43.7	10–12/0–3
Right auricle (low)	9.1	40.0	
Right pulmonary vein	19.9	87.8	10–16/minus 4
Left auricle	12.2	54.0	3–7/0–4
Right ventricle	10.2	45.0	200/10–20
Coronary sinus	3.3	15.0	5–8/0–2
Femoral artery	13.5	59.8	
Oxygen capacity:	22.4 vol. %	....	.....
Oxygen consumption:	212 cc. per minute	....	.....
Peripheral blood flow:	5.3 L. per minute	....	.....
Effective pulmonary flow:	2.0 L. per minute	....	.....
Right to left shunt:	3.3 L. per minute	....	.....

in 1888. An excellent drawing of this anomaly is to be found in Peacock's book, "On Malformations of the Human Heart," published in 1866.[23] Blalock[24] reports that he found a right aortic arch in 144 of 610 cyanotic patients who came to surgical treatment. The great majority of these cases were presumably instances of the tetralogy of Fallot.

Despite this apparently high incidence of right aortic arch with cyanotic heart disease there are surprisingly few cases in the literature which are presented in sufficient detail to be of value for statistical purposes. (Table II.) Although the clinical diagnosis of right-sided aortic arch is simple, that of the associated intracardiac anomalies is not. For this reason, only those cases are included in Table II which were proven by postmortem examination.

Although the fourteen cases here summarized represent all those unearthed by a search of the literature, there is no question that there are many more which are unreported.

It may be noted in Table II that when right aortic arch is associated with other cardiac anomalies, they are invariably lesions causing central cyanosis. Ten of the fourteen are the tetralogy of Fallot. There is one case of Eisenmenger's complex, one of a variant of the Eisenmenger's complex and one each of tricuspid atresia and levocardia with multiple anomalies.

Furthermore, in thirteen of the cases (92 per cent) the aorta arises either in whole or in part from the right ventricle. The one exception is the case of tricuspid atresia.

These figures confirm the experience of Brock and Campbell[25] who state that they have not found a right-sided aortic arch with any proved case of pure pulmonary stenosis. In addition, none of the reported cases of cyanosis caused by pulmonary stenosis with interatrial septal defect and reversed shunt have been associated with right-sided aortic arch.[1,4,5,26]

AN ILLUSTRATIVE CASE

Many of the difficulties attendant upon the establishment or exclusion of overriding aorta are illustrated in the following case report:

M. D., a twenty-nine year old woman was admitted to the Mount Sinai Hospital for the first time on May 10, 1948. She was said to have been cyanotic at birth but was then well until eight years of age when, following an attack of pertussis, she developed dyspnea, cyanosis and fatigue. Her activities from that time on were considerably restricted, with the development of deep cyanosis and dyspnea on exertion.

Physical examination disclosed a moderately well developed, cyanotic woman who was dyspneic on the slightest exertion. The fingers and toes were clubbed. The heart was not enlarged to percussion. A loud harsh systolic murmur was heard all over the precordium, loudest at the left third and fourth interspaces. The cardiac rate was 100; blood pressure was 110/65. The liver edge was barely palpable and slightly tender but there was no hepatic pulsation.

Laboratory findings were: hemoglobin 14.5 gm. per 100 cc; red blood cell count 7,370,000; white blood count and differential smear normal.

Electrocardiogram revealed right axis deviation with small Q2 and Q3; aVR showed small Q and tall R; unipolar precordial leads showed small Q and low R over the right side of the chest up to V1. From V1 through V6 there was a small R, deep S pattern. These findings were interpreted as indicating right ventricular hypertrophy and clockwise rotation of the heart.

Chest x-ray showed no infiltration in either lung. (Fig. 1.) The pulmonary vessels were small and sparse. The heart was globular in configura-

tion and the right border was prominent. The waist of the heart was narrow and the aortic knob was small. In the oblique projections the hila were unusually lucent and there was evidence of right ventricular enlargement.

Circulation time study revealed the following: The arm to periphery time (calcium gluconate) was 6.8 seconds; the ether time was 5.8 seconds, associated with tingling of lips and fingers.

While drawing a blood specimen during cardiac catheterization from the right auricle, the color of the blood was seen to change abruptly, suggesting a shunt of oxygenated blood from the left auricle. Neither the aorta nor pulmonary artery were entered. Pressures were not measured. The oxygen content of the various specimens was as follows: coronary sinus 1.1 volumes per cent, right auricle (1) 7.0, right auricle (2) 4.8, right ventricle 6.3, superior vena cava 7.2, right brachial artery 11.4 volumes per cent (64 per cent saturated).

Angiocardiogram in the left anterior oblique position (Figs. 2 and 3): (Reported by Dr. Marcy L. Sussman): "Showed the left auricle to contain diodrast practically immediately after it entered the right auricle, suggesting strongly the presence of an interatrial septal defect with a right to left shunt. The right auricle and ventricle were dilated. The pulmonary valve was narrowed. The main pulmonary artery was small. The branches were smaller than usual but within normal limits. The aorta visualized early in the sequence but this could be accounted for by the interatrial septal defect. The findings are best explained by the presence of interatrial septal defect with pulmonic stenosis."

The diagnosis lay between tetralogy of Fallot with interatrial septal defect and pulmonary stenosis with interatrial septal defect. The inability to establish the presence or absence of overriding aorta left the diagnosis in doubt. On June 9, 1948, a Blalock-Taussig anastomosis was performed between the left subclavian and left pulmonary artery by Dr. Arthur S. W. Touroff. After operation a harsh to-and-fro murmur was heard over the pulmonary area for only a few days. A microplethysmogram[38] shortly after the operation indicated the presence of an extracardiac arteriovenous communication.

After leaving the hospital the patient noted a marked increase in her exercise tolerance. Fifteen months after operation, however, she noted an abrupt increase in her symptoms of dyspnea and cyanosis. Three months later she

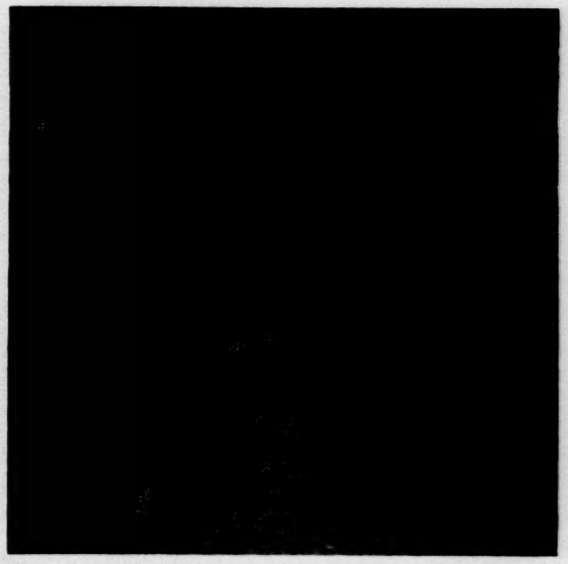

FIG. 1. Roentgenogram of the chest taken in 1948 during the patient's first admission to the hospital.

was readmitted to the hospital because of incidental abnormal vaginal bleeding.

The patient was readmitted on January 25, 1951. Cyanosis and clubbing were marked. The physical examination of the heart was unchanged, except that some observers heard a diastolic murmur in the left infraclavicular region. The blood pressure was 110/70. Chest x-ray showed no change since 1948.

Fluoroscopy of the heart revealed the left ventricular apex to be elevated above the left leaf of the diaphragm. There was a convexity in the region of the left pulmonary artery as seen in the right lateral projection, but in the postero-anterior projection this segment was concave. The main pulmonary artery branches were normal in size with slight decrease in the smaller vascular markings of the lungs. In the right anterior oblique position the shadow of the right ventricle encroached upon the retrosternal area.

Blood studies: Hemoglobin 17.5 gm. per 100 cc., red blood count 7,340,000; hematocrit 63 per cent.

Cardiac catheterization:[39] The catheter was passed through a left antecubital vein into the right auricle, thence into the right lung field through an interatrial septal defect and a pulmonic vein. The right ventricle was intubated but neither the aorta nor pulmonary artery were entered. Right ventricle to ear circulation time, using Evans blue solution, was six seconds. (Table III.)

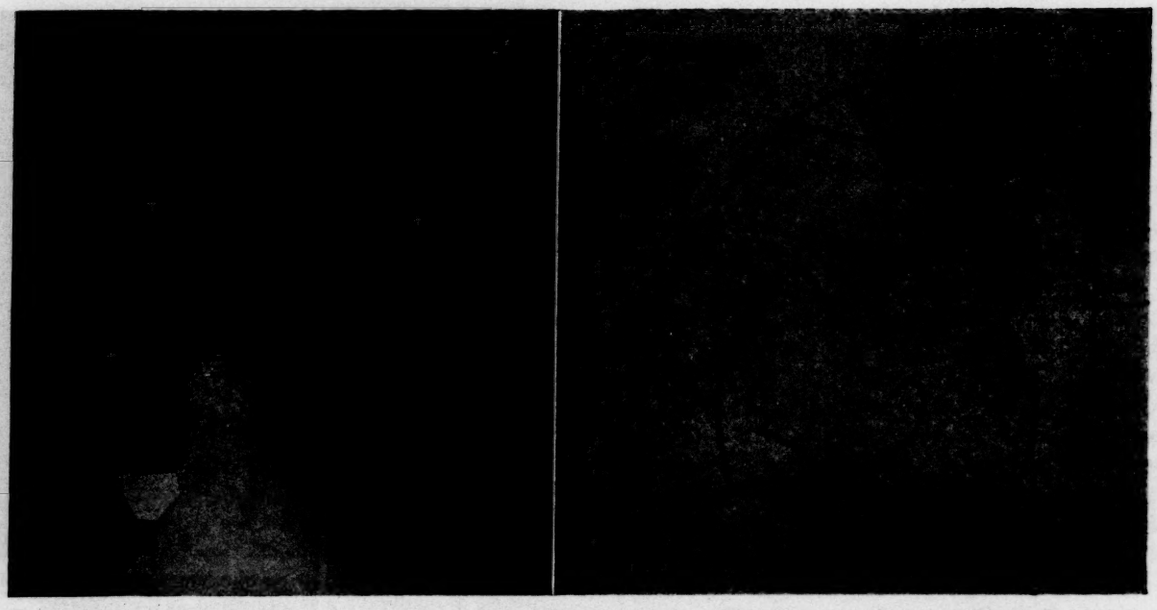

FIG. 2. Angiocardiogram taken in the left anterior oblique projection. This film, one of the earliest in the series, shows diodrast in the superior vena cava and right atrium.

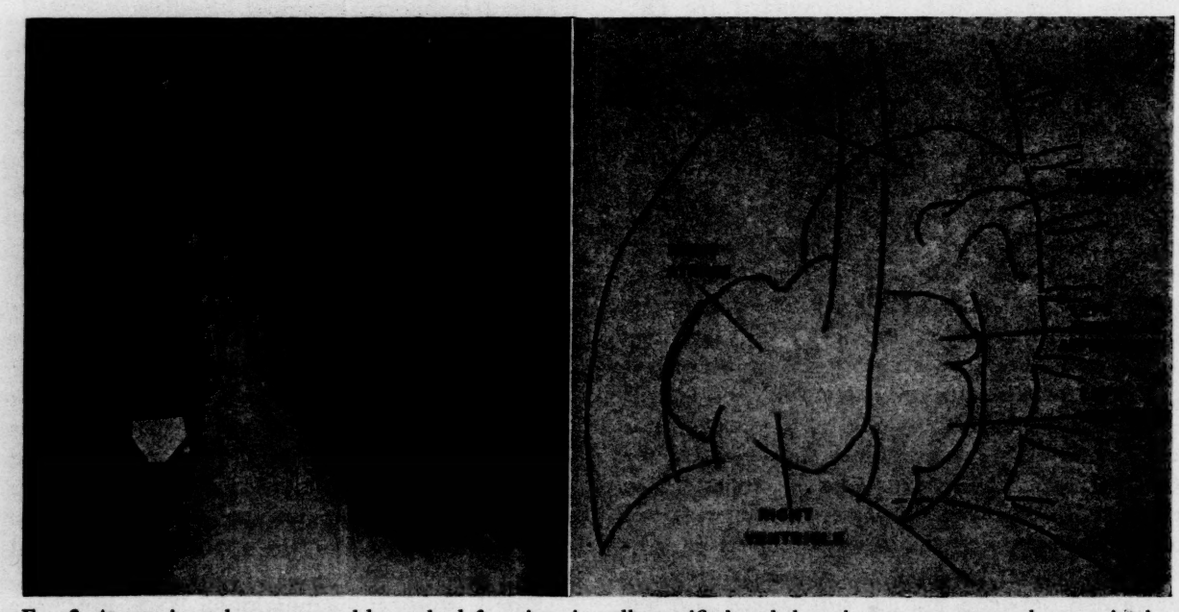

FIG. 3. Approximately one second later the left atrium is well opacified and there is some contrast substance in the aorta and pulmonary artery.

Angiocardiogram (Figs. 4, 5 and 6): (Reported by Dr. Sigmund Brahms): This was made with the patient in the postero-anterior position. Six films were made at half-second intervals and the last six at one-second intervals. There was evidence of interatrial septal defect with right to left shunt as manifested by opacification of the left atrium within one-half second after diodrast appeared in the right atrium. When the left atrium was initially visualized, the left ventricle was not significantly opacified. It was impossible to state whether or not the aorta could be seen on this film. About a second later the left ventricle was well opacified and at that time the density of the aorta was greatest for this series. The pulmonary arteries were small. Although the great vessels arising from the aorta were well delineated, the artificial

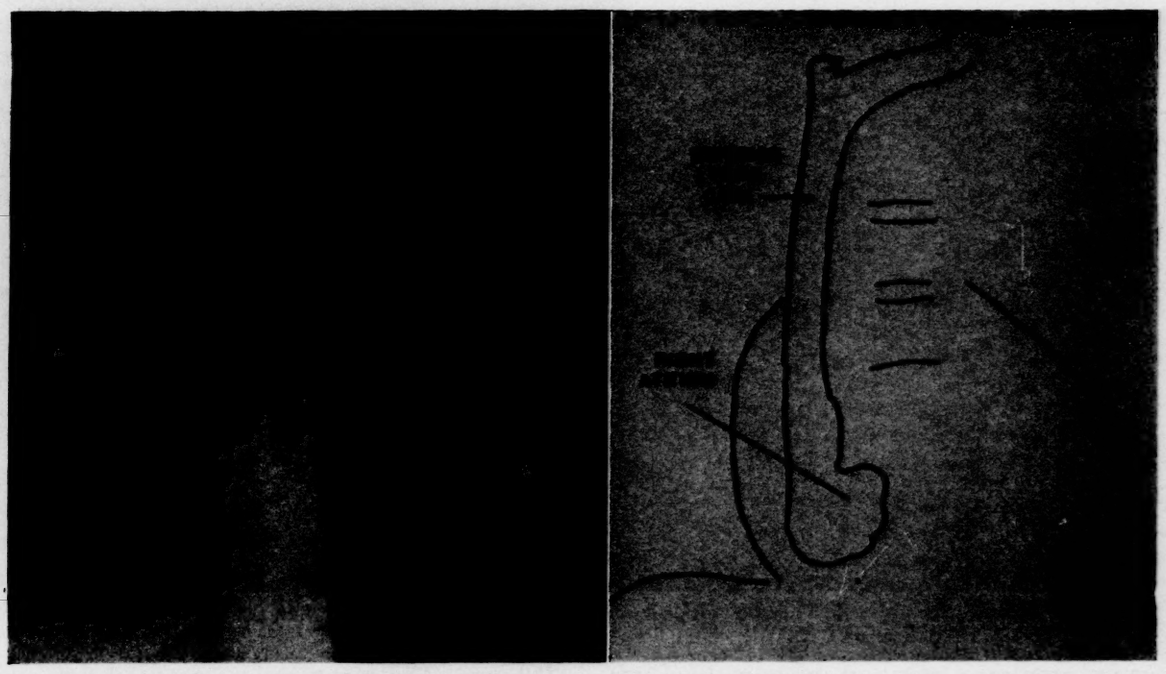

FIG. 4. Angiocardiogram made in 1951 in the postero-anterior position. The first film of the series demonstrates the diodrast entering the right atrium.

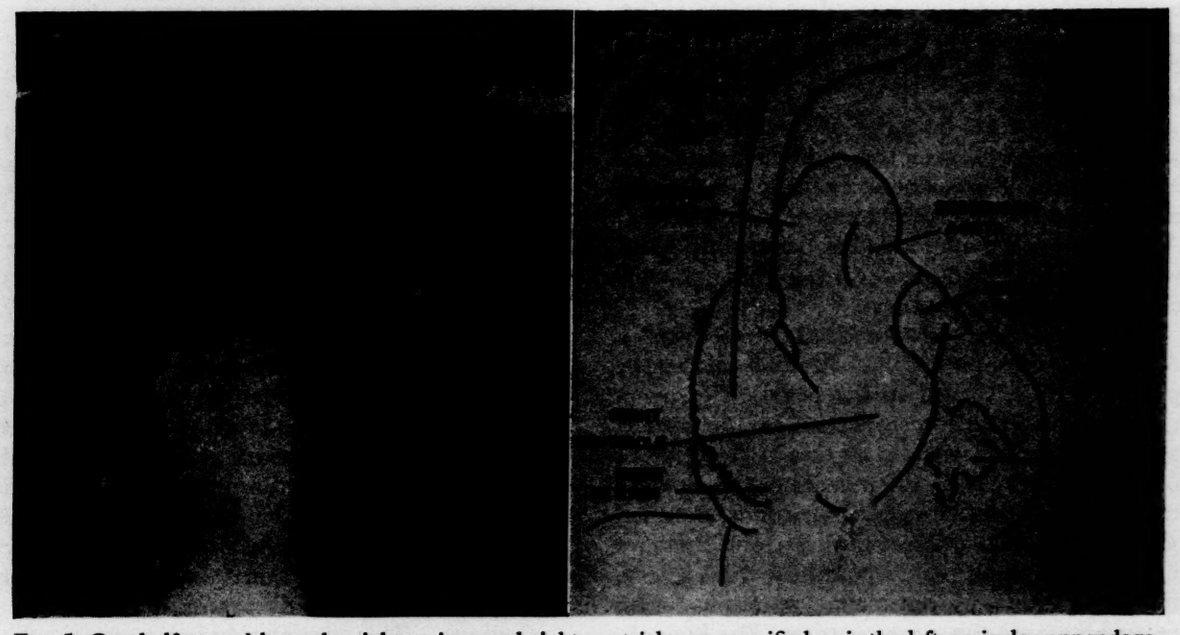

FIG. 5. One-half second later the right atrium and right ventricle are opacified as is the left auricular appendage. A few streaks of the opaque substance are seen in the left ventricle. The aorta is also visualized. There is no evidence of opacification of peripheral pulmonary vessels.

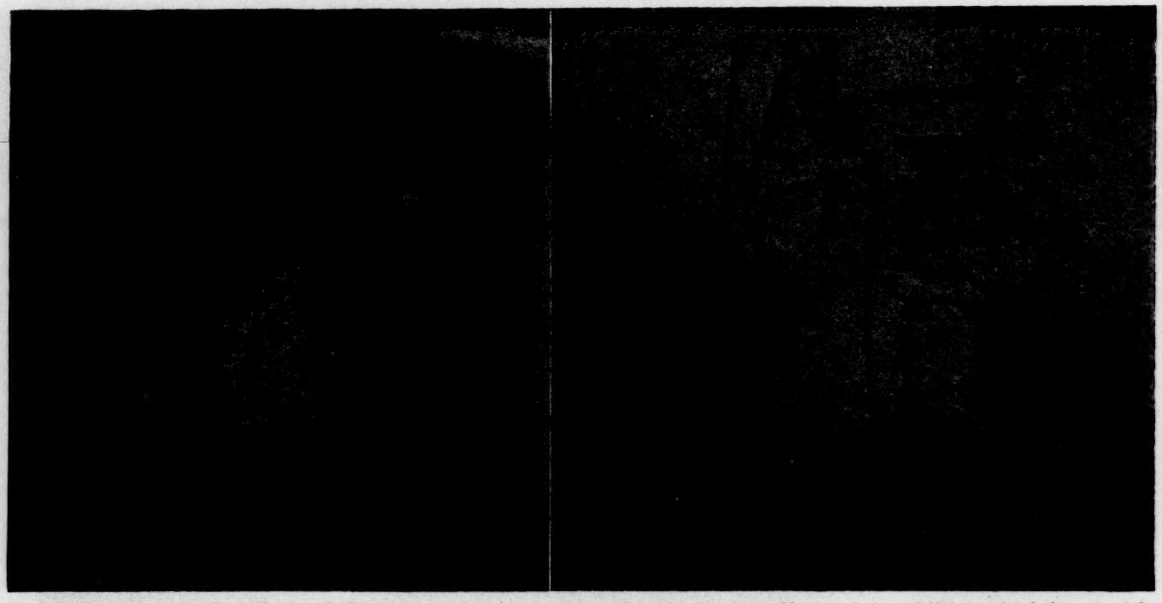

FIG. 6. One second after Figure 5. This shows the features seen in the previous film and, in addition, the left ventricle and great vessels are well seen.

ductus arteriosus was not visualized. These findings were thought to indicate the presence of an overriding aorta in addition to interatrial septal defect with a significant right to left shunt.

The opinion that initial visualization of the aorta had occurred by virtue of overriding of the aorta was based on the assumption that the density of the aorta was greater than that of the left ventricle.

She had several episodes of weakness associated with twitching of the right arm and leg. Multiple small phlebotomies were performed in an effort to relieve the excessive polycythemia. A pulmonary valvulotomy was being considered when she died suddenly during the performance of a mild exercise test.

Until the time of her death there was a difference of opinion as to the diagnosis, particularly in regard to the question of overriding aorta. The interpretation of the second angiocardiogram was an argument in favor of overriding. However, the normal right ventricle to ear circulation time of six seconds, coupled with the marked difference in systolic pressure between the right ventricle and brachial artery, indicated that no significant communication existed between the two structures. The Blalock-Taussig anastomosis was not thought to be functioning.

Postmortem examination was performed by Drs. Jacob Dyckman and Daniel Kushner. The heart did not appear grossly enlarged, weighing 250 gm. The right atrium was dilated and markedly hypertrophied. The foramen ovale was widely patent, measuring 2 cm. in diameter. The right ventricular wall was greatly thickened. The posterior leaflet of the tricuspid valve was atretic and anomalous in insertion, forming a separate chamber which communicated freely with the auricle but not with the main ventricular chamber. The pulmonary valve ring was 1.3 cm. in diameter. The pulmonary valve was formed by three small cusps which were fused, leaving only two pinpoint apertures, one about 1 mm. in diameter, the other admitting a horsehair. The pulmonary artery beyond the valve was of normal diameter. The pulmonary vessels were otherwise normal. The aorta arose entirely from the left ventricle. The interventricular septum was intact. The anastomosis between the left subclavian and pulmonary artery was completely occluded by a firm organized thrombus in the subclavian. A single bronchial artery, about 2 mm. in diameter, was identified but special injections to delineate bronchial arteries were not done. *Anatomic diagnosis:* Pulmonary valvular stenosis; interatrial septal defect; Ebstein's anomaly of tricuspid valve.

Comment. This case clearly indicates that the ordinary clinical examinations are sometimes unable to establish or exclude the presence of overriding aorta. In particular, a right to left shunt through an interatrial septal defect may be of such magnitude as to lead to a shortening

of the circulation time equal to that caused by an overriding aorta. This may be reflected in early visualization of the aorta during angiocardiography. It is often impossible to ascertain by angiocardiography if premature visualization of the aorta occurs by way of an overriding aorta or via an interatrial septal defect. This case is illustrative of the fact that it is erroneous to assume that overriding of the aorta is present because opacification of that vessel occurs at a time when the left ventricle is not visualized. It has been emphasized previously[40] that the ventricles, especially the left, are not usually well seen in angiocardiograms.

SUMMARY

Methods designed to establish the presence of overriding aorta in congenital heart disease have been reviewed. Conventional studies involving the speed of the circulation, including angiocardiography, may prove a right to left shunt without indicating its site. Pressure relationships obtained during cardiac catheterization may be relied upon only to *exclude* overriding aorta.

Passage of a catheter into the aorta from the right ventricle is undoubtedly the most reliable method of proving the diagnosis of overriding aorta. A rapid right ventricle to ear circulation time is strongly in favor of this anomaly. With rare exceptions, the presence of a right-sided aortic arch in a cyanotic patient indicates that the aorta arises in whole or in part from the right ventricle.

The difficulties attendant upon the diagnosis or exclusion of overriding aorta are illustrated by a case report.

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The Influence of Age, Anesthesia and Cerebral Arteriosclerosis on Cerebral Vascular Activity to CO_2*

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A METHOD capable of quantitatively predicting the degree of cerebral vascular sclerosis is greatly needed in clinical medicine. The problem consists of two parts: (1) the determination of the presence of generalized vascular sclerosis before the onset of any symptoms of cerebral dysfunction; (2) the separation of patients with symptoms of senility into three groups, namely, those with sufficient structural disease in the vessels to account for the cerebral degenerative changes, those with cerebral degeneration without structural vascular disease, and those with a combination of degenerative changes in the brain and structural vascular disease.

Previous studies on senility,[1] myxedema[2] and anesthesia[3–5] have shown that a low cerebral blood flow may be present in the absence of structural changes in the blood vessels. If one could cause full vasodilatation in the vessels of the brain, one might separate the patients with decreased blood flow due to structural changes in the vessels from those with decreased blood flow due to other causes. The purpose of this study was to determine whether vasodilatation caused by CO_2 inhalation would allow the separation of these two classes of patients.

The following groups were studied: (1) The cerebral blood flow and metabolism of *normal* people were measured over a wide age range. The degree of vasodilatation caused by breathing 5 per cent and 7 per cent CO_2 was determined. (2) The cerebral blood flow, cerebral metabolism and CO_2 responsiveness were measured in a group of patients with *cerebral vascular disease* demonstrated clinically by stroke. (3) The effect of *thiopental anesthesia* on CO_2 responsiveness was determined. (4) Observations were made on patients with *degenerative brain disease without clinical evidence of generalized arteriosclerosis.*

METHOD

Cerebral blood flow (CBF) was measured by the N_2O technic as described by Kety and Schmidt,[6] and modified by Scheinberg and Stead.[7] Oxygen differences ($A\text{-}VO_2$) determined by the method described by Hickam and Frayser[8] were made on the integrated arterial and cerebral venous blood specimens, respectively. Cerebral oxygen consumption ($CMRO_2$) was calculated by multiplying the respective CBF and $A\text{-}VO_2$ difference.

Following the control CBF, the patient breathed either 5 per cent or 7 per cent CO_2 for four minutes. The ensuing increase in CBF was then estimated, utilizing the earlier observations of others[9,10] showing that neither 5 per cent nor 7 per cent CO_2 significantly change $CMRO_2$. For example, if the initial CBF was 60 cc./min./100 gm. brain and the initial $A\text{-}VO_2$ difference was 6.0 vols. per cent, the product of these—or the $CMRO_2$—would be 3.6 cc. of O_2 per minute per 100 gm. brain. If, following four minutes' CO_2 inhalation, $A\text{-}VO_2$ difference narrowed to 4.0 vols. per cent, then CBF could be calculated to be—assuming constant cerebral metabolism—$\frac{3.6}{4.0}$ or 90 cc./min./100 gm. brain.

Eight patients were anesthesized with 0.6 to 1.5 gm. of sodium pentothal given intravenously over a ten- to thirty-minute period. A second CBF was measured by the N_2O method while the subject was under anesthesia. This was again followed by four minutes' inhalation of 5

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per cent or 7 per cent CO_2 and the increase in CBF was calculated as indicated previously.

In those patients who were anesthetized clear airways were maintained by oropharyngeal intubation and anoxia did not occur. Depth of anesthesia was sufficient so that noxious stimuli were no longer perceived and cerebral metabolism was reduced by at least 33 per cent.

In all patients blood pressure was measured by the auscultatory method with the arm held at heart level. Most patients were studied in a fasting state; a few had had a light breakfast.

TABLE I*
REACTIVITY TO CO_2 IN NORMAL SUBJECTS

	CBF†	A-VO_2	$CMRO_2$	CBF	
				5% CO_2	7% CO_2
Group I					
12 subjects age 21 to 35 (average age 29)	62 SD ± 11	6.6 SD ± 1	4.0 SD ± 0.4	105 SD ± 20	139 SD ± 14
Group II					
10 subjects age 35 to 45 (average age 40)	57 SD ± 12	6.4 SD ± 0.9	3.5 SD ± 0.3	86 SD ± 14	120 SD ± 21
Group III					
7 subjects age 50 to 76 (average age 64)	55 SD ± 9	6.7 SD ± 0.9	3.7 SD ± 0.4	77 SD ± 24	119 SD ± 25
Mean	59 SD ± 11	6.6 SD ± 0.9	3.8 SD ± 0.4	89 SD ± 23	129 SD ± 20

* There is no significant change in CBF, A-VO_2 difference of $CMRO_2$ in the various age groups. In group I the total CBF response to 5% and 7% CO_2 may be different from groups II and III ($p = 0.1$).

† CBF = cerebral blood flow in ml./min./100-gm. brain; A-VO_2 = arterial-cerebral venous oxygen difference in volumes per cent; $CMRO_2$ = cerebral metabolic rate of oxygen consumption in ml./min./100-gm. brain; SD = standard deviation of the mean.

RESULTS

Normal Subjects of Different Ages. Studies were made on twenty-nine subjects in whom no evidence of vascular disease could be detected by careful examination of optic fundi and peripheral vessels, and in whom there was no past history nor present indication on physical examination of hypertensive cardiovascular disease. (Table I.) The younger normals (age twenty to thirty) were made up of healthy young doctors (three), physically normal schizophrenics (four), patients with duodenal ulcer (three) and patients with mixed psychoneurosis (two). Patients in the thirty-five to fifty age group included mainly patients with schizophrenia and peptic ulcer who appeared healthy. The normal elderly patients were the most carefully selected patients in this study. These patients were in the hospital for minor illness or for diagnostic survey. All were unusually alert and were active, energetic working people in essentially good health. None had a history or evidence of hypertension or arteriosclerosis.

One is impressed by the small change in cerebral blood flow and vascular reactivity to CO_2 which occurs with aging. The vascular reactivity in the subjects above thirty-five years of age was less than that of the younger subjects ($p = 0.1$). We assume that figure would be a significant one if the series were extended. It is to be emphasized that these patients were selected for two reasons: (1) their age, and (2) the fact that when age[10,11] is the primary criterion of selection the blood flow and metabolism will be reduced. This may explain the difference in the results in this series and those reported by Fazekas.[10]

TABLE II
COMPARISON OF NORMAL SUBJECTS AND PATIENTS WITH STROKES

	CBF	A-VO_2	$CMRO_2$	CBF	
				5% CO_2	7% CO_2
Stroke					
10 subjects (average age 59)	35 SD ± 6	7.2 SD ± 2	2.6 SD ± 0.9	49 SD ± 14	61 SD ± 21
Normals					
29 subjects (average age 46)	59 SD ± 11	6.6 SD ± 0.9	3.8 SD ± 0.4	89 SD ± 23	129 SD ± 20
p Value	.01	n.s.*	.01	.01	.01

* Not significant.

Patients with Strokes. The prime requirement in this group was a clear-cut history, with residual neurologic defects of varying degree, of a cerebral vascular accident. Unless this was present all collateral evidence pointing to generalized arteriosclerosis elsewhere was not deemed sufficient to make a diagnosis of cerebral arteriosclerosis. All of these patients had long-standing hypertension, arteriosclerotic retinopathy, evidence of peripheral vascular disease, often had calcification noted by x-ray in the great vessels of the chest and abdomen, and several had concomitant diabetes mellitus. None were in congestive heart failure or uremia. The data are given in Table II. The cerebral blood flow[1,10,12] and metabolism and response to CO_2 are all reduced.

Patients with Organic Brain Disease without Stroke. Eight patients with organic brain disease as manifested by gross disturbances in memory, thought and personality were studied.

In none of these patients could the diagnosis of cerebral arteriosclerosis either be made or excluded by physical examination. None had significant retinal changes, hypertension or evidence of peripheral vascular disease. Two patients, I. K. and H. H., had air encephalograms which showed cortical atrophy. The data in this group are given in detail in Table III and are compared with the findings in the stroke group. No significant change in CBF or $CMRO_2$ was found between these two groups—findings which are in agreement with those previously reported.[1,11] The CBF following 5 per cent CO_2 was greater in the senile group ($p > 0.05$). There were fewer patients tested with 7 per cent CO_2 but the flow was again greater than in the patients with strokes ($p > 0.1$). The response to both 5 per cent and 7 per cent CO_2 in the senile group was not only greater than in the stroke group but was also more variable. This suggests that this group was less homogeneous in population. It seems possible that in some of the senile patients cerebral arteriosclerosis existed which we were unable to detect clinically. In the eight senile patients there were three responses (two after 5 per cent and one after 7 per cent CO_2) which were outside of twice the standard deviation of the mean of the patients with stroke. Seven of the twelve responses to CO_2 in the senile group were beyond the greatest response to CO_2 found in the entire group with stroke. Both the senile and stroke groups show an essentially equal reduction in both CBF and $CMRO_2$ when compared with normal older people ($p = 0.01$). The stroke group, however, reacted poorly to 5 per cent CO_2 ($p = 0.02$) when compared to older normal people, while the senile group showed no significant change from older normal subjects.

TABLE III*

SENILE DEMENTIA

Patient	Age	CBF	A-VO_2	$CMRO_2$	Total CBF		Increase CBF	
					5% CO_2	7% CO_2	5% CO_2	7% CO_2
L. L.	75	36	10.0	3.9	..	93	..	57
D. A.	81	36	6.5	2.3	55	74	19	38
H. B.	75	30	7.1	2.1	37	61	7	25
F. B.	76	45	5.9	2.7	73	..	28	..
H. H.	56	40	7.4	2.9	63	97	23	57
M. P.	56	47	6.2	2.9	101	..	54	..
M. T.	82	52	6.2	3.2	73	..	21	..
I. K.	57	39	6.7	2.6	75	110	36	71
Mean of senile group	70	40.6	7.0	2.8	68	87	27	50
		SD ± 7	SD ± 1.3	SD ± 0.6	SD ± 20	SD ± 19	SD ± 15	SD ± 18
Stroke, 10 subjects	59	35	7.2	2.6	49	61	14	29
Normal old subjects (7)	64	55	6.7	3.7	77	119	26	63

* There is no significant difference in CBF or $CMRO_2$ between the stroke and senile groups. Both are different from normal old subjects in these factors ($p = .01$). Cerebral vascular reactivity (increase in CBF) after 7% CO_2 and total CBF after both 5% and 7% CO_2 is significantly changed from the stroke to the normal old subjects ($p = .01$, .02 and .01 respectively). There is no significant difference in cerebral vascular reactivity to both 5% and 7% CO_2 between the senile and the normal old age group. The differences in reactivity between the senile and the stroke groups to both 5% and 7% CO_2 are of borderline significance ($p = .1$ to .05).

TABLE IV

EFFECT OF THIOPENTAL ON CO_2 REACTIVITY IN EIGHT SUBJECTS

	Control	Anesthesia	p Value
CBF	61 SD ± 12	46 SD ± 7	.01
A-V O_2 Difference	6.3 SD ± 1	4.8 SD ± .7	.01
$CMRO_2$	3.6 SD ± .4	2.2 SD ± .3	.01
CBF after CO_2*	105 SD ± 29	71 SD ± 20	.01

* Three subjects received 7% CO_2 and five received 5% CO_2. The same CO_2 percentage was used before and during anesthesia in each individual subject.

Normal Patients under Thiopental Anesthesia. Tables IV and V show the data on eight healthy-appearing schizophrenic patients without demonstrable vascular disease. The data on each patient include double studies of CBF, $CMRO_2$ and reactivity to CO_2—both before and during anesthesia. The data show that when $CMRO_2$ is greatly depressed by anesthesia, there is a significant decrease in responsiveness to CO_2. The data do not allow us to conclude whether this decreased responsiveness is due to depression of cerebral metabolism or to the direct depressant action of thiopental on cerebral vessels.

TABLE V

COMPARISON OF CO_2 RESPONSE IN ANESTHESIZED SUBJECTS AND PATIENTS WITH STROKES

	Anesthesia	Stroke	p Value
CBF	46 SD ± 7	35 SD ± 6	.01
A-V O_2 Difference	4.8 SD ± .7	7.2 SD ± 2	.01
$CMRO_2$	2.2 SD ± .3	2.6 SD ± .9	n.s.*
CBF after 5% CO_2	60 SD ± 14	49 SD ± 14	n.s.
7% CO_2	90 SD ± 12	61 SD ± 21	.05

*Not significant.

COMMENTS

At the present time we believe that normal responsiveness to CO_2 makes diagnosis of generalized cerebral arteriosclerosis highly unlikely. We already knew at least one condition, namely, anesthesia, which reduces cerebral vascular reactivity when no structural vascular disease is present. A poor response, therefore, may or may not indicate cerebral vascular disease. The technic appears to have practical application in separating some of those patients with dementia due to severe cerebral arteriosclerosis from those patients with dementia due to primary parenchymal brain degeneration.

SUMMARY AND CONCLUSIONS

1. Cerebral vascular reactivity to CO_2 is high in normal adult people of all age groups, and there is only gradual reduction in reactivity with the normal aging process.

2. In severe cerebral vascular disease, cerebral vascular reactivity to CO_2 is greatly reduced.

3. The response to CO_2 is altered by thiopental anesthesia deep enough to reduce the cerebral metabolic rate by 40 per cent.

4. Cerebral vascular reactivity to CO_2 can be utilized to separate certain patients with senile dementia due to primary parenchymal brain degeneration from dementia secondary to cerebral vascular disease. A normal high increase in CBF after CO_2 makes the diagnosis of generalized cerebral vascular disease highly improbable, while a poor response may or may not indicate its presence.

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Tests for So-called Capillary Fragility of the Skin and the Significance of Positive Tests in Vascular Disease*

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WHEN the tourniquet test or other tests for capillary fragility are positive, it is customary to assume that there is a defect in the capillaries. Wintrobe[1] in a discussion of the causes of bleeding reports positive "tourniquet tests" in: (1) Certain infections and allergic states which have damaged capillary endothelial cells; (2) thrombocytopenic purpuras in which there are too few platelets to support the capillaries under pressure; and (3) scurvy in which there is a deficiency of intercellular cement substance. These diseases characterized by spontaneous hemorrhages may be differentiated from each other and from other hemorrhage diseases by a study of coagulation time, bleeding time, prothrombin time, clot retraction and platelet counts. Positive tourniquet tests are usually not obtained in hemophilia, hyperheparinemia, idiopathic afibrinogenemia and vitamin K deficiency.

Other hemorrhagic diseases, grouped by Wintrobe as generalized vascular disorders, are hereditary hemorrhagic telangiectasia, the purpuras associated with advanced renal or hepatic disease, snake venom purpura, non-thrombocytopenic purpura of drug poisoning, purpura senilis or cachectica, orthostatic purpura, Cushing's syndrome and Ehlers-Danos syndrome. However, no reference is made to positive or negative tourniquet tests in this group. He does not include in his dissertation on hemorrhage the purpura or eyeground hemorrhages observed in some patients with hypertensive vascular disease and diabetes. This study was made to determine the incidence of the positive tourniquet test or positive capillary fragility in this group of vascular disease.

METHODS

First we attempted to evaluate the methods and technic. Ideally, a satisfactory test should tell us every time that the test is positive that the capillaries of the body possess a subnormal resistance to rupture. Investigators have employed many different clinical methods to obtain a reliable test but unfortunately, exaggerated claims have been made for the reliability of some methods, many of which are complicated and laborious. Here is a sample:[2] "Mark off 2 circular areas 6 cm. in diameter in each antecubital space. The blood pressure cuff is inflated to 35 mm. Hg and maintained there for 15 minutes. After this, count all petechiae within the 2 areas. One hour later, put the cuffs up to 50 mm. Hg and the petechial index is calculated as follows: To the number of petechiae occurring at 35 mm. Hg multiplied by 2, add the additional number occurring at 50 mm. Hg. Based upon the petechial index, capillary fragility is considered to be normal if the index is 8 or less, increased or abnormal if the index is 13 or more. It is borderline or probably abnormal if the index is 12." This method assumes that counting petechiae accurately elicits the degree of capillary fragility but as pointed out by Hines and Parker,[3] "The usual method of petechiae counting in a given area of skin may fail to give an accurate picture of the amount of hemorrhage. Patients often show large ecchymoses and even the petechiae vary greatly in size." Others have also written about the inaccuracy of an end point in determining capillary fragility but in spite of this, the same investigator often draws a definitive conclusion while he questions the accuracy of the test. The

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Göthlin and Rumpel-Leede–Hess methods are one of a group which exposes the skin capillaries to varying amounts of intracapillary pressure and depends for an end point on the degree of capillary rupture. Based on this same theory other tests with only minor differences in the technic have been described. The Wright[4] modification of the Rumpel-Leede test and the Schweppe[5] modification are examples. In our opinion accurate conclusions are more difficult when we use methods which depend on increasing the intracapillary pressure. After much preliminary study we discarded the positive pressure methods (Rumpel-Leede type) because petechiae from the positive test may persist for a week and prevent accurate readings when comparative tests are desired. Inaccuracies observed with the cuff method were: The petechiae had a tendency to appear first along the course of superficial veins or immediately adjacent and distal to the pressure cuff; excessive hairiness or excessive relaxation of the skin is more common in the area tested. We chose a negative pressure test for our study because it was speedy, only a small skin area was required and because we could select a suitable area of skin. Because of simplicity and accuracy we used a modification of the convenient spring-actuated cup as devised by da Silva-Mello.[6] The head was of transparent plastic which permitted observation of the amount of skin elevation in the cup during the test. The cup had an inside diameter of 20 mm. The rim was 3 mm. in width and rounded. The technic and standardization of this method had been thoroughly worked out by Dalldorf[7] who used it in an investigation of subclinical scurvy in children. He considered the appearance of gross petechiae at a pressure less than 20 mm. of Hg as an indication of abnormality. In his extensive study he emphasized the variation in results caused by individual differences in skin texture, pigmentation and skin thickness and he also observed that readings differed when the tests were applied to different parts of the body and at different times of the day. He believed that the test was clinically valuable only when readings were made in large enough numbers to submerge the individual differences encountered, or when serial tests were made over a long period of time. In our study we found that tests in the antecubital fossae (the traditional cuff zone) were not accurate. It had been previously shown by Cutter[8] and others that areas of the body not ordinarily used might be more suitable for the test than the cuff zone. After extensive experience the interscapular area of the back was chosen because of absence of skin folds, relative hairlessness, uniformity of skin texture and freedom from superficial veins. Even though more constant results were obtained in this area, single readings were not always adequate to rule out surface variations. Our tests were made with readings at minus ten, twenty and thirty (representing mm. of Hg) in closely adjacent areas. In this way each area served as a control to its neighbor, and the test could be repeated if there were marked area variations. The readings at different pressures gave a more sensitive indication of minor changes. If one reading was equivocal, greater or less pressure with other readings might reveal a clearer result. Evaluation of improvement was also easier when studying the effect of three levels of pressure. Sometimes, we were able to count petechiae. In more cases the small hemorrhagic areas were confluent and counting was impossible. Therefore, we adopted a method, previously described by Hines and Parker,[3] of labeling the results negative, one plus, two plus, three plus or four plus. With the patient sitting in a good light in a normally heated room free from drafts, a slight coating of vaseline was placed on the interscapular area of the back. The plunger was set at the desired pressure level and the cup was placed gently but firmly against the back prior to release. During the test the cup was maintained by negative pressure alone in a constant position using care to prevent twisting, tilting or unusual pressure. The elevations of the skin at the beginning and at the end of the test were compared; if a decrease was seen, it was an evidence of error. It might be due to lack of pressure on the cup at the start of the test, lack of skin lubrication, improper plunger lubrication or small cracks in the instrument (bowl or neck). After an interval of one minute the plungers were returned to their original position to restore normal atmospheric pressure in the bowl prior to removal. Readings were made one minute after removal of bowl to permit the erythema to subside. In most cases an accurate petechia count was not possible; but when the petechiae could be counted, a result of ten or more was considered abnormal. The stronger positive tests showed confluent hemorrhages of varying degrees of intensity, labeled as previously described one plus, two plus, three

plus or four plus. The negative test was one with no hemorrhage or with small petechiae, less than ten in number.

RESULTS

Two hundred sixty-nine adults have been studied to learn more about the incidence and dependability of positive tests in normal adults and in patients with diseases which show spontaneous hemorrhages in the skin or retina. The test has been recorded as positive only after making at least six determinations with a suction cup on successive days. The positive pressure (Rumpel-Leede) method was also used when results were doubtful. Negative tests were those with no hemorrhages after the suction cup was applied or when less than ten petechiae were found after the tourniquet test. Discrepancies were not rare. If the test were slightly positive on one day and negative the next day and slightly positive on the third day, it would be recorded negative.

TABLE I
INCIDENCE OF POSITIVE CAPILLARY FRAGILITY TESTS

Diagnosis	No.	Positive	
		No.	Per cent
Normal (under 30 years of age)	102	2	2
Non-vascular disease with normal blood pressure (30 to 80 years of age)	150	18	12
Vascular disease with normal blood pressure	46	8	17
All patients with arterial hypertension	116	58	50
Uncomplicated diabetes mellitus	15	1	7
Diabetes complicated by vascular disease	27	18	67
Acute myocardial infarction with normal blood pressure	19	6	30
Acute myocardial infarction with hypertension	5	2	40

Table I shows our findings in 102 normal young adults. Only 2 per cent of this group showed positive tests and the plasma ascorbic acid levels and ascorbic acid saturation levels in those with positive tests were normal. Twenty of the 102 normals had clinical evidence suggesting vitamin C deficiency but none of the twenty showed positive capillary fragility tests. The table shows that 14 per cent of an older group (167 varying in age from thirty to eighty) had positive tests even though their blood pressures were no higher on the average than the average of the younger group. The table also reveals that the percentage of positive tests is greatly increased to 50 per cent in the older group when arterial hypertension is present.

TABLE II
INCIDENCE OF POSITIVE CAPILLARY FRAGILITY IN PATIENTS WITH SPONTANEOUS RETINAL HEMORRHAGES

Diagnosis	No. of Patients with Retinal Hemorrhage	Patients with Positive Capillary Fragility	
		No.	Per cent
Non-hypertensive or non-vascular	5	2	40
Arterial hypertension	15	8	54
Diabetes and arterial hypertension	10	8	80

Patients with uncomplicated diabetes mellitus have positive tests in only 7 per cent; but when vascular disease such as arteriosclerosis or hypertension is associated with diabetes, capillary fragility is positive in 67 per cent of cases. When hypertension is associated with myocardial infarction, there is a slightly greater incidence than in non-hypertensive myocardial infarction.

Table II presents the results in a small series of patients who had spontaneous retinal hemorrhages. In this group patients with diabetes and hypertension showed 80 per cent positive tests and others a lower but significant number of positive tests.

COMMENTS

Previous studies by Hines and Parker have also shown that there is a high incidence of positive tests in patients with various types of vascular disease, especially when combined with diabetes. It was also shown in those studies that capillary fragility could be eliminated in some patients by large doses of ascorbic acid; although at times the results were inconstant in patients with vascular disease, uniform and quick improvement was noted in patients with scurvy.

Increased capillary fragility in hypertension had been demonstrated also by Griffith and Lindauer[9] in their work with rutin. They

showed that capillary fragility was increased in about 18 per cent of 265 cases of hypertension. They also observed that patients with increased capillary fragility were predisposed to apoplexy, retinal hemorrhages and premature death. In the majority of their patients rutin was capable of eliminating capillary fragility. Donegan and Thomas[10] also demonstrated abnormally increased capillary fragility in patients with arteriosclerosis, hypertension and diabetes. The highest incidence was found in diabetics who had retinopathy. Beaser, Rudy and Seligman[11] using Wright's method have shown that in the diabetic hypertensive patient there is a greater incidence of increased capillary fragility as the age increases. These authors reported that vitamin C was ineffective in improving capillary fragility in diabetic patients but they used only 200 mg. of ascorbic acid per day whereas 5 gm. was required in many of the patients in our series.

It is interesting to speculate on the relationship between the cause of spontaneous hemorrhages and positive capillary fragility tests in scurvy and in vascular disease. There is evidence that the capillary defect in scurvy is due to collagen deficiency. No such deficiency has been demonstrated in vascular disease. However, the elimination of the positive capillary fragility test in both scurvy and vascular disease by large doses of ascorbic acid suggests a similar defect in the capillaries in these two diseases.

From time to time hemorrhage in arteriosclerotic disease processes has been studied, not so much from the standpoint of cause but as to its effect. For example, Winternitz[12] has suggested that hemorrhage may be the focal point of an atherosclerotic patch or intimal hemorrhage may initiate and precede the development of thrombi. Our interest is not only with hemorrhages which occur spontaneously in the skin and viscera, but also with patients who show no hemorrhages in the skin but do exhibit positive capillary fragility tests from the trauma of the testing device. It is well known that not all patients with vascular disease show this tendency to hemorrhage and there is no deficiency known to be capable of explaining hemorrhage in one patient with vascular disease and not in another. Paterson[13] believes that the sequence of events in the production of intimal hemorrhage is as follows: (1) there is endarteritis with vascularization of the intima; (2) an atheromatous plaque degenerates and softens the intercapillary stroma and (3) there is rupture of the newly formed intravascular capillary. Paterson makes this conclusion because discrete intimal capillaries, atheroma and intimal hemorrhage have been found in practically every coronary artery showing recent thrombosis. He suggests that this chain of events which leads to thrombosis is precipitated by damage to the endothelial lining from extravasation of blood into the intima. Wartman[14] and Winternitz[12] agree that intimal hemorrhages result from rupture of capillaries which are derived from the backflow of blood from intimal defects. These pathologic findings explain the local problem when the coronary or cerebral artery is involved but they do not explain the tendency to hemorrhage in the skin caused by fragility tests in the same patient with coronary thrombosis or cerebral thrombosis or in patients with hypertension. Spontaneous retinal hemorrhages, common in diabetes and vascular diseases, also cannot be explained by their theory. Paterson suggests that newly formed capillaries are formed as a part of endarteritis in an atheroma in the coronary or cerebral vessel but there is no evidence to suggest such a change in skin capillaries in any disease. Our studies suggest that there is a correlation between the defect which allows hemorrhages in the skin from capillary fragility tests and spontaneous hemorrhages from fragile capillaries in various viscera.

SUMMARY

Positive capillary fragility or positive tourniquet tests are terms used loosely to describe intracutaneous hemorrhage produced by standardized doses of trauma (suction or venous compression). These tests for capillary fragility are crude and cannot be performed accurately by counting petechiae. Sources of error are numerous and can be overcome only by making numerous tests on different days. In the recorded results of this paper intracutaneous hemorrhage in the test is graded one to four plus. Inconstant and inconclusive results have been discarded.

A higher incidence of positive tests is found in older patients.

Patients with diabetes mellitus which coexisted with hypertension or other vascular disease showed an extremely high incidence of positive capillary fragility tests and this corresponds to the well known high incidence of spontaneous retinal and skin hemorrhages in such patients.

All patients with hypertension and also those

with arteriosclerotic disease without hypertension showed moderately high incidence of positive fragility tests.

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Chronic Hyperosmolarity of the Body Fluids with a Cerebral Lesion Causing Diabetes Insipidus and Anterior Pitutiary Insufficiency*

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THE most commonly encountered cause of elevated concentrations of sodium and chloride in the extracellular fluid is dehydration.[1,2] The increase in effective osmotic pressure of the extracellular fluids, or possibly the associated cellular dehydration, is the stimulus which elicits the subjective sensation of thirst.[3,4] Thirst therefore ordinarily provides a safeguard against relative or absolute deficits of water in the fully conscious patient. The precise location(s) in the central nervous system wherein the complete regulation of the thirst mechanism resides is not known. In any event it is clear from the studies of Holmes and Gregerson in dogs[3] that considerable individual variations in the sensitivity of the thirst mechanism occurs and also that the amount of water voluntarily ingested, in response to hypertonicity, is not entirely determined by the amount required to dilute injected salt to isotonicity. Thus individual differences in the sensitivity of the thirst mechanism in man might be expected. It is also possible that adaptation or conditioning to chronically abnormal concentrations of extracellular salt may occur. However, in an individual who is too ill to make his needs for water known or who suffers from a clouded sensorium large deficits of water can be present without his complaining of thirst. In a case to be presented of a patient who suffered from a chronic hypernatremia, some defect in the thirst mechanism was undoubtedly present although the precise nature of this defect is not clear.

Severe dehydration with consequent hypernatremia and hyperchloremia may acutely develop in patients who suffer large renal losses of water in excess of salt due to unrecognized diabetes insipidus[5] or to acute toxic nephrosis.[6,7] Similar severe dehydration may occur if high protein diets are administered with insufficient water to sick individuals.[8] Mac Carty and Cooper[9,10] reported hypernatremia in several patients with cerebral lesions; they did not seriously consider unrecognized diabetes insipidus or a disturbed thirst mechanism as a cause of the hypernatremia in their cases. Whether certain neurologic lesions can lead to hypertonicity of the body fluids without a disturbed thirst mechanism or diabetes insipidus is not known. If so, it would be necessary to postulate cerebral control of cellular osmolarity. For this there is as yet no evidence.

In this article data will be presented on a patient who suffered from a cerebral lesion which was responsible for the development of diabetes insipidus. Further, she exhibited chronic hyperchloremia and hypernatremia. The fact that the patient also presented definite clinical and laboratory evidences of anterior pituitary insufficiency is of further interest since it has been claimed that anterior pituitary insufficiency ameliorates diabetes insipidus. Inasmuch as Gaunt et al.[11] suggested that pitressin and cortisone act generally antagonistically on the renal tubular absorption of salt and water, the acute effects of these agents were studied. Two patients

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with uncomplicated diabetes insipidus were studied for comparison.

MATERIALS AND METHODS

E. K., a twenty-eight year old white woman, was admitted to the hospital for the first time in March, 1949. Her complaints were progressive fatigue, dizziness and fainting on standing, weakness, complete amenorrhea, poor memory, mild intolerance to cold, pallor and dryness of the skin, and periods of excessive thirst. In 1940 after the birth of her first child she had a severe postpartum hemorrhage. In 1941 she became pregnant again; during this pregnancy she felt continuously fatigued and chronically nauseated. Delivery was uncomplicated in 1942. She claimed to have had one episode of uterine bleeding after delivery but thereafter became amenorrheic. At this time she began to experience much chronic fatigue, weakness and dizziness. No hot flashes were present. In 1946 marked thirst and polyuria developed. The patient stated she "drank at least two pails of water" in each twenty-four-hour period and "was up half the night drinking and urinating." These symptoms continued for about five months and then gradually subsided without treatment. However, since that time she claimed to have periods of excessive thirst but these periods never lasted more than a day or two. She stated she usually drank ten to fifteen glasses of water per day in addition to fluids at mealtime. During her illness it was noted that her memory was poor and thinking processes retarded. At times she would lapse into a "sleepy-stuporous" state from which, however, she could be easily aroused. The patient's mother had to assume most of the responsibility for the management of the household.

Physical examination revealed pale, fine, dry skin and little body hair. The skin was characteristic of that seen in patients with anterior pituitary insufficiency. Axillary hair was completely absent and pubic hair was scant. The blood pressure was 78/68 mm. Hg lying; 70/50 mm. Hg sitting, and unobtainable on standing. The hands appeared slightly puffy and the breasts were mildly atrophic. The visual fields were normal. The remainder of the examination was unremarkable.

Preliminary laboratory studies revealed normal skull and abdominal x-rays. The spinal fluid was normal. Mild anemia was present (3.7 million red blood cells/cu. mm. and 78 per cent hemoglobin). The basal metabolic rate was minus 27 per cent of normal. A four-hour glucose tolerance test revealed a fasting blood sugar of 69 mg. per 100 ml. blood and 97 mg., 110 mg., 77 mg. and 76 mg. at hourly intervals thereafter. The Robinson-Power-Kepler "water test" (part 1) was strongly positive (night volume: 435 ml.; largest day volume: 80 ml.). Four hours after the administration of 25 mg. ACTH* the circulating eosinophils numbered 260 (initial count 240). The 17-ketosteroid excretion was 2.0 mg. per twenty-four hours.

On two occasions the patient was deprived of water to tolerance; at the end of these periods of severe dehydration the specific gravity of the urine was 1.007 and 1.008. The latter was the highest specific gravity observed at any time; usual values were 1.004 to 1.006. The non-protein nitrogen of the blood was always within normal limits. An Addis count of the urinary sediment was normal. The phenolsulfonthalein excretion in two hours was 60 per cent. The diagnosis of anterior pituitary insufficiency and diabetes insipidus seemed well established by clinical and laboratory evidence.

In October, 1950, it was surprisingly discovered that the serum sodium was 161 m.Eq./L. and the chloride 116 m.Eq./L. Since that time numerous sodium and chloride levels have been obtained. When not receiving preparations of posterior pituitary, the serum sodium varied between 150 and 165 m.Eq./L. and the serum chloride between 110 and 120 m.Eq./L.

Two patients with uncomplicated diabetes insipidus also were studied. D. S. was a thirty year old woman with typical diabetes insipidus of unknown cause who required the use of posterior pituitary powder to control the disorder. W. L., a forty-five year old man, had diabetes insipidus consequent upon an attack of encephalitis. He used pitressin® tannate in oil for control.

The three patients were hospitalized for study and previous medications were discontinued. So as to evaluate thirst mechanisms, all were allowed fluids *ad libitum* throughout the study. Accurate records of their intake of fluid and output of urine were made. Their diets contained approximately 8 gm. of sodium chloride per day throughout the periods of study. Following a control period of two to four days the patients were given 0.3 ml. pitressin† intramuscularly

* A product of the Armour Laboratories.

† Product of Parke, Davis & Co.

every four hours day and night for three days. The pitressin was then abruptly discontinued. The postpitressin period continued for three to four days. E. K. was studied during two periods. Cortisone, 25 mg. per day (12.5 mg. twice daily, orally), was administered throughout one

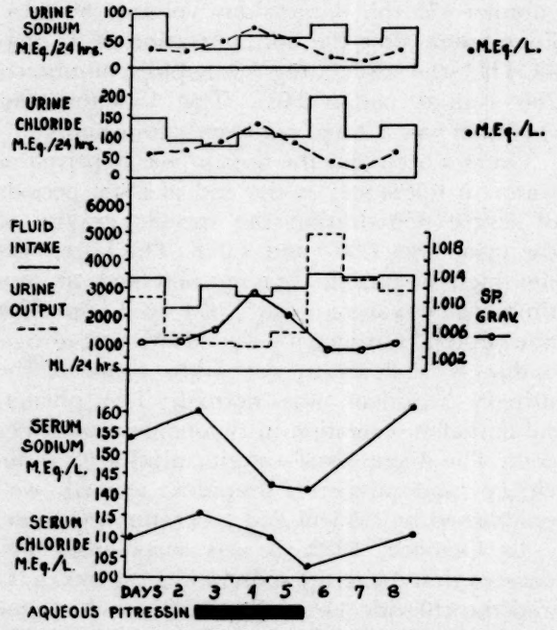

FIG. 1. Data on effects of pitressin (0.3 ml. intramuscularly every four hours) in E. K. when not maintained on cortisone.

period; it was omitted during the other. Blood serum was obtained at intervals for sodium and chloride determinations. The sodium content of the blood and urine were determined with the Barclay internal standard flame photometer. The normal range for blood sodium in our laboratory is 135 to 142 m.Eq./L. Serum and urine chlorides were determined by the methods of Whitehorn[12] and Volhard and Harvey,[12] respectively.

RESULTS

Figure 1 summarizes the data on E. K. when she was not on cortisone. With pitressin administration the urine output promptly diminished and the specific gravity of the urine rose from previously low levels. Interestingly enough the voluntary intake of fluid remained relatively constant throughout the entire study. If a constant daily insensible water loss of 800 ml. is assumed, then about 3 L. of water were retained during the interval of pitressin administration. This is more than sufficient to account for the fall in concentration of sodium and chloride to normal. In fact an increase of only 1.7 L. of extracellular water would account for the observed fall in sodium and chloride concentrations. It is likely, but unproved by these

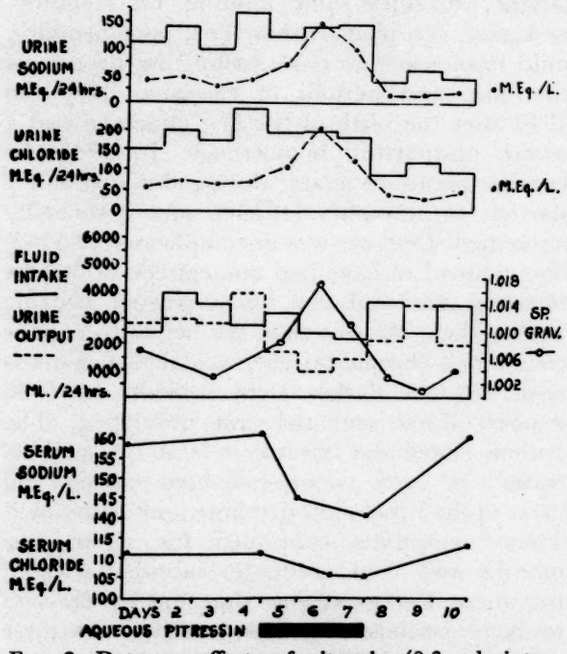

FIG. 2. Data on effects of pitressin (0.3 ml. intramuscularly every four hours) in E. K. when on constant amounts of cortisone (25 mg. orally per day).

studies, that water also moved intracellularly. No striking change in chloride or sodium excretion occurred during or after pitressin administration. In the postpitressin period a negative water balance promptly developed and, undoubtedly as a consequence of this, the high concentrations of sodium and chloride in the serum were re-established.

The study was repeated on E. K. but during this period she was maintained on 25 mg. of cortisone per day. The data are presented in Figure 2. During the administration of pitressin effects were observed which were entirely similar to those obtained under identical circumstances without cortisone. However, in the postpitressin period a sharp reduction in urine sodium and chloride excretion occurred and water diuresis was delayed. The concentrations of sodium and chloride in the serum returned to the previously high values. The rise in their concentration appeared mainly to be due

to increased renal tubular reabsorption of sodium and chloride.

In a separate study the effect of larger doses of cortisone (100 mg. per day for four days) on the intake and output of fluid was examined. From Table 1 it is seen that no exaggeration of the

TABLE 1*

Day	Medication	Fluid Intake (ml.)	Urine Output (ml.)	Specific Gravity	Serum Na (mEq./L.)	Serum Cl (mEq./L.)	Serum HCO_3 (mEq./L.)
1	None	3,360	2,250	1.006	156	114	29.6
2	None	3,390	2,880	1.002			
3	None	2,960	1,805	1.005			
4	Cortisone, 100 mg.	2,250	1,150	1.007			
5	" " "	2,480	1,860	1.003			
6	" " "	2,800	1,270	1.004	159	110	30.1
7	" " "	2,300	†	1.006			
8	None	3,300	1,840	1.004			
9	None	2,700	2,060	1.003			

* Study of acute effects of 100 mg. of cortisone per day on the intake of fluid and output of urine of patient E. K.
† Part of this specimen lost.

diabetes insipidus occurred and no alteration in ability to concentrate urine resulted during this interval.

The effects of the administration of pitressin for three days to two patients (W. L. and D. S.) with uncomplicated diabetes insipidus are presented in Figures 3 and 4. Under the circumstances of these studies there was a mild unsustained increase in sodium and chloride excretion with pitressin administration; however, the result was least striking in D. S. (Fig. 4.) The most definite effect appeared in the postpitressin period when, in both instances, a sharp decrease in renal excretion of salt occurred. The effect was entirely similar to the results obtained on E. K. while she was maintained on constant amounts of cortisone.

In contrast to E. K. who drank relatively constant amounts of fluid, the voluntary intake of fluid in the patients with uncomplicated diabetes insipidus promptly decreased as their output of urine decreased. Also in both of these patients, and in E. K. while on cortisone, diuresis of water did not abruptly reappear when the pitressin was discontinued. It seemed as if a certain amount of salt retention was required before maximal polyuria and thirst were established. Pitressin tannate in oil (1.0 ml.) was given twice to W. L. (Fig. 3); a chloruretic and natriuretic effect was noted.

COMMENTS

Hypertonicity of the body fluids has been noted in association with different lesions of the central nervous system in different locations by Allott[13] (hemorrhage between the frontal lobes, hemorrhage into right internal capsule,

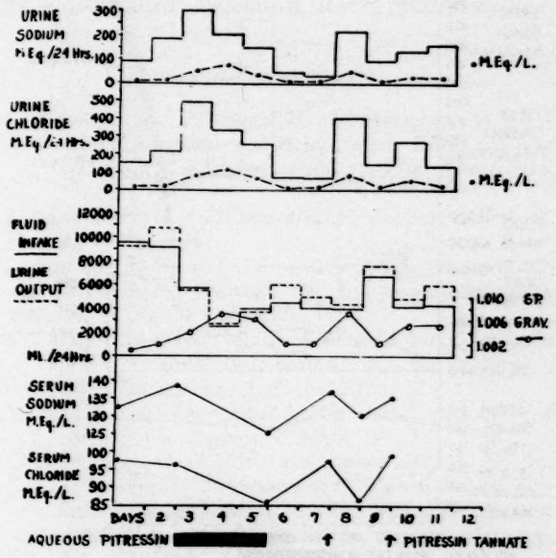

FIG. 3. Data on effect of pitressin (0.3 ml. intramuscularly every four hours) in W. L. with uncomplicated diabetes insipidus. On the eighth and tenth days 1.0 ml. pitressin tannate in oil was administered.

tumor in region of choroid plexus and tuberous sclerosis), by Cooper and Mac Carty[9,10] (ligation anterior cerebral arteries, surgery for pituitary tumors, thrombosis left middle cerebral artery) by Sweet and his associates[14] (prefrontal lobotomy) and by Peters[15] (surgery for craniopharyngioma). The fundamental cause of the electrolyte disturbances may not be entirely identical in these different cases.

Several mechanisms of origin are theoretically possible. First, diabetes insipidus (lack of antidiuretic hormone, [ADH]) might exist. The thirst mechanism could be fundamentally intact but the need for water not expressed because of a clouded sensorium. The result would be severe dehydration which, of course, is the most common cause of hypertonicity. If uncorrected by ADH or by large amounts of water, death would result since the disorder would be a progressive one. If large amounts of fluids were not administered, the usual picture of diabetes insipidus, with its intense polyuria, would not be apparent. It is possible that two of the aforementioned cases were on this basis.[9,15]

Second, diabetes insipidus could exist in a conscious patient whose thirst mechanism (response to hypertonicity) was so poorly integrated because of a neurologic lesion that a rather chronic state of dehydration and hypernatremia would result. It is likely that patient

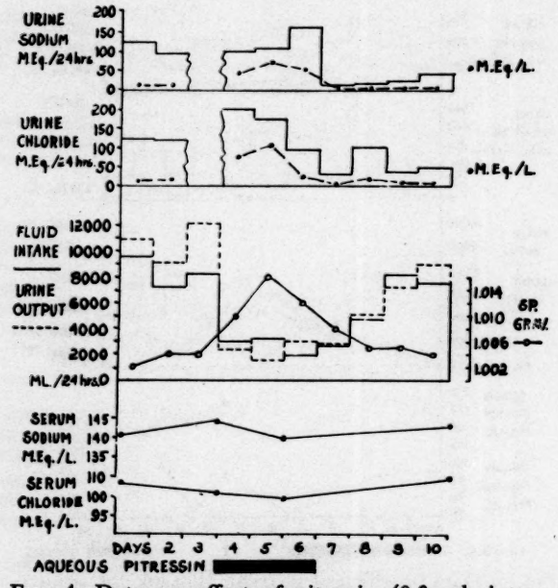

FIG. 4. Data on effect of pitressin (0.3 ml. intramuscularly every four hours) in D. S. with uncomplicated diabetes insipidus.

E. K. falls into this category. With or without pitressin E. K. voluntarily drank relatively constant amounts of water. If the stimulus to thirst is hypertonicity of the extracellular fluids, then a defect in the thirst mechanism must be present in our patient. It is likely that several of the reported cases that survived for rather prolonged periods also were on this basis.

Disruption of the thirst mechanism by certain neurologic lesions as the sole cause of the state of hypertonicity is also conceivable. Slight but significant increases in serum sodium were observed by Stevenson, Welt and Orloff[16] in obese rats following the production of bilateral lesions in the ventromedian region of the hypothalamus. They felt that the cause of the disturbance was a relative state of dehydration. "The lower water/food intake ratio implied a deficit in the neural mechanism responsible for thirst and its alleviation." However, the speed of development and the intensity of the hypernatremia as described in some of the cases in man makes it rather unlikely that this mechanism is the only factor operative in the genesis of the disorder. On the other hand, disturbances of the complex mechanism of thirst may be relatively common in a variety of neurologic lesions.

Finally, direct nervous system control of the osmolarity of the intracellular and extracellular fluids is possible. An increase in cellular osmolarity would result in establishment of a new equilibrium with an increase in extracellular concentration of sodium and chloride. Central nervous system control of renal function would be implicit in this concept. However, there is no direct evidence to support this idea. Whether the antidiuretic hormone could correct an abnormality of this nature, if it were shown to exist, is not known.

There have been conflicting reports on the effect of pitressin on the renal excretion of sodium and chloride.[17,18] Differences in result undoubtedly reflect variations in experimental procedure. Roemmelt and associates[19] suggest that the natriuretic and chloruretic actions of pitressin can be demonstrated only when the urinary concentrations of sodium and chloride are initially below their respective maxima. Our subjects with uncomplicated diabetes insipidus were not previously loaded with water prior to the administration of pitressin and probably were in a mild state of hydropenia. Pitressin appeared to cause a transitory loss of sodium and chloride, possibly as response to previous mild dehydration.

On the other hand, in E. K. no chloruretic or natriuretic effect of pitressin was noted either with or without cortisone. (Figs. 1 and 2.) Rather marked salt loss with pitressin might have been anticipated if its natriuretic and chloruretic actions were unopposed by adrenal cortical activity. No such effect was seen. Further, the diabetes insipidus of E. K. was not exaggerated by the administration of 100 mg. of cortisone daily for four days. (Table 1.) Since the intensity of the polyuria in diabetes insipidus is largely conditioned by the solute load delivered to the distal tubule,[20] it is likely that more prolonged administration of cortisone would be necessary to exaggerate the disorder. In any event no direct antagonism between ADH and cortisone on the renal tubular absorption of water or salt could be demonstrated in these studies.

In both patients with diabetes insipidus and in E. K. on cortisone a striking retention of sodium and chloride promptly occurred with discontinuance of pitressin. The duration of the antidiuretic action of aqueous pitressin is

considered to be less than five hours,[4] yet salt retention rather than polyuria characterized the first forty-eight hours after pitressin administration. While this might suggest that a disturbance in salt metabolism is more fundamental in diabetes insipidus than polyuria, the full significance of the phenomenon is not apparent. It may represent the response to a temporarily greater gradient in concentration of salt between the tubular urine and plasma. But that this effect represents a secondary response to overhydration during pitressin administration seems unlikely since other observations indicate that an expanded extracellular volume diminishes the tubular resorption of salt.[21]

That adrenal cortical activity is necessary for the postpitressin retention of salt is shown by the fact that the phenomenon did not occur when E. K. was not receiving cortisone. Since the effect appeared in E. K. with the administration of constant amounts of cortisone an actual increase in cortical activity during this period need not be assumed in the two patients with uncomplicated diabetes insipidus. The presence of cortisone merely permitted the reaction to take place.

SUMMARY

A case is presented of a patient with diabetes insipidus and anterior pituitary insufficiency who exhibited chronic hypernatremia and hyperchloremia and a defective thirst mechanism. The hypertonicity of the body fluids was entirely alleviated with pitressin. After discontinuance of pitressin the hyperosmolar state promptly recurred, mainly through a process of salt retention when cortisone was available and through water diuresis when cortisone was not available. In a separate study the administration of 100 mg. of cortisone per day for four days did not aggravate the diabetes insipidus and the administration of pitressin did not cause increased renal losses of salt. No direct antagonism between ADH and cortisone on the renal tubular absorption of water or salt was demonstrated.

Marked postpitressin retention of sodium and chloride was noted in two patients with uncomplicated diabetes insipidus. Salt retention rather than diuresis of water characterized the first forty-eight hours after the use of pitressin for three days. It is suggested that adrenal cortical activity, but not necessarily increased activity, permits this reaction.

Some of the cases reported in the literature of hypernatremia in patients with neurologic lesions may represent examples of diabetes insipidus and a disturbed thirst mechanism.

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Diabetic Nephropathy*

Kidney Biopsy and Renal Function Tests

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THE increasing frequency with which renal diseases have been encountered in recent years as a complication of diabetes mellitus presumably is due chiefly to the fact that insulin treatment has considerably extended the duration of life of diabetics.

The early literature states that the following three lesions of the kidney are of frequent occurrence in diabetes mellitus: (1) chronic pyelonephritis, (2) arteriosclerosis and (3) arteriolosclerosis (nephrosclerosis) with hypertension; these disorders may be present separately or in various combinations. With regard to the nephrosclerosis of diabetics, it was stressed several times in the early literature that it differed from the ordinary clinical picture of nephrosclerosis in presenting with marked proteinuria and nephrotic edema.

In 1936 Kimmelstiel and Wilson[20] described eight cases of diabetes mellitus with characteristic nodular hyaline masses in the glomeruli. They termed this change *intercapillary glomerulosclerosis*. They considered the lesions to be sclerotic thickenings of the intercapillary connective tissue (the mesangium), and emphasized that these glomerular changes were present in a characteristic clinical syndrome: longstanding diabetes mellitus with nephrotic syndrome and hypertension. Since then both clinicians and pathologists have published many papers on this subject,[3,7,12,14,21,23,24,28,29,32] all of which largely confirm the observation made by Kimmelstiel and Wilson.

Many authors, however, question whether this is an absolutely specific diabetic renal disorder and whether the nodular glomerular change described by Kimmelstiel and Wilson is in fact the specific diabetic pathologic basis of the syndrome.[1,2,14,19,26,28] Several authors[1,7,14,17,21,28,32] have reported that they have demonstrated glomerular changes of the type described by Kimmelstiel and Wilson in a few patients who must be supposed not to have been diabetics. Even though it is always difficult in a single case definitely to exclude the possibility that the patient has been a diabetic, there is apparently hardly any doubt that the nodular Kimmelstiel-Wilson change is not absolutely specific of diabetes mellitus; however, it is so rare in non-diabetics that several authors[1,7,21,28] have maintained that the demonstration of Kimmelstiel-Wilson nodules in the glomeruli can be considered *almost* pathognomonic of diabetes mellitus.

Another question of interest in this connection is whether *diffuse* hyaline changes in the basement membranes of the glomeruli—without nodules—can be considered of diabetic origin. Some authors[7,12,13,17,21] have included such changes in their descriptions of diabetic changes in the kidneys, and both Fahr[12] and Bell[7] accept the view that in addition to the nodular diabetic glomerular lesion there is a diffuse form which is of much more frequent occurrence. Even though diffuse changes of this type are found very frequently in chronic glomerulonephritis, nephrosclerosis and chronic pyelonephritis, and in hypertension in non-diabetics, and despite the fact that it may be impossible to demonstrate the diabetic origin of such changes in the individual case, we can hardly deny the possibility that a diffuse glomerular change may be of diabetic origin. It is, for instance, maintained by Laipply, Eitzen and Dutra[21] that it is possible histologically to distinguish the diabetic-diffuse hyalinization from diffuse hyalinization of other

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etiology. The nodular and diffuse forms may possibly represent different phases of the same process, and both Bell[7] and Henderson, Sprague and Wagener[14] consider that the nodular form develops from the diffuse lesion by continuous splitting of the basement membrane. It may be mentioned in this connection that several authors[1,7,21,29] are unable to accept Kimmelstiel and Wilson's assumption that the characteristic nodules are localized *inter*capillarly, as they have not been able to demonstrate the presence of any supporting tissue (mesangium) between the capillary loops; these authors consider that the nodular Kimmelstiel-Wilson changes develop from the basement membrane.

With regard to the pathogenesis of the Kimmelstiel-Wilson changes, there has been considerable discussion as to whether they might be due to specific vascular lesions in diabetics, *inter alia* owing to the almost constantly occurring diabetic retinopathy in patients with Kimmelstiel-Wilson changes.[4,5] It is true that Ashton, who has studied this question in detail, was unable to demonstrate the identity of the microaneurysms underlying the diabetic retinopathy with the Kimmelstiel-Wilson changes; nevertheless he considers that "an aneurysmal dilatation can be demonstrated in connection with some of the nodular masses in intercapillary glomerulosclerosis," and that "the histogenesis of the glomerular lesions is comparable in all respects to the pathological process in the retina."

Histochemical examinations of Kimmelstiel-Wilson lesions[1,6,29,31] have not contributed significantly to the elucidation of the nature of the changes.

There has been considerable discussion among clinicians whether it is possible on the basis of the clinical picture to establish the diagnosis of intercapillary glomerulosclerosis *intra vitam;* apparently this is not always the case.[2,7,14,26,27,28] It is true that there is a group of patients in whom this diagnosis can be made with a fair degree of probability: elderly patients, often women, with prolonged, generally mild diabetes mellitus, severe proteinuria, renal edema, hypertension and diabetic retinopathy. It has been shown, however, in large series of cases that—perhaps particularly during its initial stages—intercapillary glomerulosclerosis may be present although not suggested by the clinical picture. A recently published article by Rogers and Robbins[26] indicates that intercapillary glomerulosclerosis is wrongly diagnosed on clinical grounds in about one-third of the cases when compared with the autopsy findings. Finally, it is, of course, difficult in a single case to diagnose mixed forms with concomitant pyelonephritis, arteriosclerosis and nephrosclerosis.

A number of previous publications have reported the results of discrete renal function tests in diabetics who presented clinical symptoms of complicating intercapillary glomerulosclerosis.[11,15,16,25,30] It may be mentioned that, broadly speaking, no characteristic functional changes were found of a nature that would permit differentiation from other chronic renal diseases. The results showed a more or less pronounced decrease in glomerular filtration rate, renal plasma flow (diodrast and para-aminohippuric acid clearances) and tubular function —secretory (diodrast and para-aminohippuric acid Tm) as well as reabsorptive (glucose Tm[22]). The investigations of all these authors suffer, of course, from the uncertainty with which the clinical diagnosis of intercapillary glomerulosclerosis hitherto has been made.

The purpose of the present study was to determine whether kidney biopsy, in conjunction with specific renal function tests, can aid in the diagnosis of diabetic nephropathy, and to correlate histologically verified cases of this disease with the results of renal function tests. We report here (1) the results of kidney biopsy examinations, (2) clinical data and laboratory findings, and (3) the results of discrete renal function tests in twelve diabetics.

METHODS

Kidney biopsy was performed by Iversen and Brun's method.[18] With regard to the histologic technic and the normal histologic findings in the kidney biopsy method, reference may be made to a previously published paper.[8]

Renal function tests included the inulin clearance (C_{In}), urea clearance (C_U), endogenous creatinine clearance (C_{Cr}), para-aminohippuric acid clearance (C_{PAH}), and para-aminohippuric acid Tm (Tm_{PAH}). Technical details are given in previous publications.[9,10]

Renal function tests were made a few days after the kidney biopsy in ten of the twelve patients; in one patient (Case 2) kidney biopsy was performed immediately after admission in diabetic coma with complete anuria; renal function tests were not made in this case, as the patient died about twelve hours later. These tests were not made in another patient (Case 1)

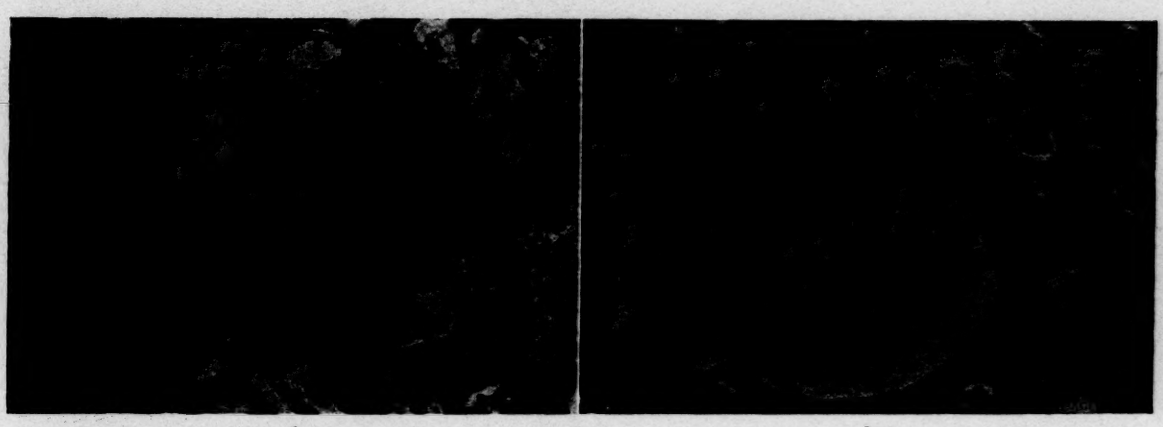

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FIG. 1. Kidney biopsy from forty-five year old man with symptoms of diabetes mellitus for six months (Case 2). Very slight glomerular hyalinization involving the basement membranes. × 280.

FIG. 2. Kidney biopsy from sixty-nine year old man with diabetes mellitus for twenty-four years (Case 6). Pronounced diffuse glomerular hyalinization in the basement membranes, thickening of the capsule, hyalinization of the vas afferens, moderate tubular atrophy and moderate increase of the interstitial connective tissue. × 280.

owing to his poor general condition; but his renal function was followed daily by the twenty-four-hour endogenous creatinine clearance.

HISTOLOGIC FINDINGS IN KIDNEY BIOPSY IN TWELVE PATIENTS WITH DIABETES MELLITUS

As examples of the histologic changes observed—presumably representing different stages of development of diabetic nephropathy—the following five cases will be mentioned in detail and illustrated by photomicrographs. (Figs. 1 to 5.)

CASE 2. N. R., (No. 1541/50) a forty-five year old man, had had symptoms of diabetes mellitus for about six months. He was admitted in diabetic coma with severe acidosis and anuria; owing to shock and pulmonary edema he died about twelve hours after admission.

Kidney biopsy immediately after admission showed only very slight changes, namely, a very slight diffuse hyalinization of part of the basement membranes in a few of the twelve glomeruli contained in the biopsy specimen which measured 6 mm. in length. Otherwise there were no glomerular changes, no changes in the tubules, no increase of the interstitial connective tissue. The vessels were normal. (Fig. 1.) Histologic diagnosis: Very slight, diffuse thickening of the basement membranes of the glomeruli.

CASE 6. J. H., (No. 1200/51) a sixty-nine year old man, had been suffering from diabetes mellitus for twenty-four years. In addition he had hypertrophy of the prostate, coliuria, hematuria, proteinuria, diabetic retinopathy and reduced renal function (the twenty-four hour endogenous creatinine clearance was reduced to about one-third of the normal).

Kidney biopsy: A biopsy specimen measuring 18 mm. in length and containing about thirty-five glomeruli was obtained. About one-third of the glomeruli were completely hyalinized (collagenic), five being almost completely hyalinized, while the remaining glomeruli showed pronounced, diffuse hyaline changes in the basement membranes; these were either collagenic or reddish yellow with the van Gieson-Hansen stain. Several glomeruli showed a varying degree of collagenic thickening of the glomerular capsule. (Fig. 2.) There were no nodular glomerular changes. There was considerable atrophy of the tubules, moderate increase of the interstitial connective tissue and a slight, non-specific chronic inflammatory infiltration around some glomeruli. Some of the slightly dilated lumina of the distal tubules contained hyaline casts. The medulla was normal. Arteries and arterioles were distinctly thickened, hyalinized. Nothing definitely suggested the presence of chronic pyelonephritis.

Autopsy sixteen months after the kidney biopsy showed almost the same picture, except for an even greater number of glomeruli that had undergone complete collagenic transformation. There were no quite typical nodules, although in some areas there were very few minute nodules staining reddish yellow with the van Gieson-Hansen stain. Nothing definitely sug-

3 4

FIG. 3. Kidney biopsy from sixty-five year old woman with diabetes mellitus for about twenty years (Case 8). Nodular-diffuse, though chiefly diffuse, glomerular changes. × 280.

FIG. 4. Kidney biopsy from sixty-two year old woman with diabetes mellitus of unknown duration (Case 10). Pronounced nodular and slight, diffuse glomerular changes. Markedly hyalinized arteriole in the upper right part of the picture. × 280.

gested the presence of chronic pyelonephritis. Histologic diagnosis: Pronounced diffuse glomerular hyalinization of the basement membranes.

CASE 8. B. P. (No. 2052/50), a sixty-five year old woman, had been suffering from diabetes mellitus for about twenty years and had been given insulin for six years. During the past eighteen months her vision had been decreasing in both eyes. She had been in the Ophthalmological Department of Kommunehospitalet for acute glaucoma but was transferred from this department to the Department of Medicine III owing to increase of the blood urea level (120 mg. per cent), proteinuria, pyuria, bacteriuria and fever. Clinical diagnosis: Chronic nephropathy (diabetic? pyelonephritic?), uremia vera, diabetic retinopathy, arterial hypertension.

Kidney biopsy: A biopsy specimen was obtained measuring 6 mm. in length and containing three glomeruli, all of the appearance shown in Figure 3: moderate, diffuse hyalinization of the basement membranes and very slight nodule formation. There were no definite tubular changes, nor were distinct vascular changes present. A single chronic pyelonephritis focus was observed. Histologic diagnosis was very slight nodular Kimmelstiel-Wilson changes and rather pronounced diffuse glomerular hyalinization of the basement membranes.

CASE 10. S. N. (No. 504/51 and 1399/51), a sixty-two year old woman, had diabetes mellitus of unknown duration. Clinical diagnosis: Diabetes mellitus, arterial hypertension, diabetic retinopathy, proteinuria, pyuria and bacteriuria. Various renal function tests were reduced to about half the normal.

Kidney biopsy: A biopsy specimen was obtained measuring 10 mm. in length and containing fifteen glomeruli; one of these showed complete collagenic transformation, ten showed typical Kimmelstiel-Wilson nodules (Fig. 4), partly collagenic, partly reddish yellow with the van Gieson-Hansen stain, while four displayed only diffuse, hyaline changes in the basement membranes. There was rather considerable atrophy of the tubules, moderate increase of the interstitial connective tissue and pronounced hyaline thickening of the arterioles. (Fig. 4.) Nothing definitely suggested the presence of chronic pyelonephritis.

Autopsy eight months after the kidney biopsy showed exactly the same changes in the kidneys as the biopsy specimen. Nothing definitely suggested the presence of chronic pyelonephritis. Histologic diagnosis: Pronounced nodular Kimmelstiel-Wilson changes and slight, diffuse glomerular hyalinization of the basement membranes.

CASE 11. A. J. (No. 1527/51), a sixty-four year old woman, had been suffering from diabetes mellitus for about sixteen years. During the past three years her vision had been decreasing. For the last few months there had been fatigue, loss of weight, dyspnea on exertion and edema of the legs. Anemia, arterial hypertension, proteinuria, hematuria and pyuria were found. Renal function was reduced to about 10 per cent. Moreover she had bilateral

cataract and arteriosclerotic and hypertensive heart disease.

Kidney biopsy: A biopsy specimen was obtained measuring 15 mm. in length and containing eighteen glomeruli, of which ten had undergone complete or almost complete collagenic transformation and showed more or less distinct segments of nodules. (Fig. 5.) Seven glomeruli presented distinct nodular changes and slight, diffuse hyalinization of the basement membranes; one glomerulus showed only slight, diffuse changes. There was rather marked atrophy of the tubules, some showed dilated lumina (containing hyaline casts) around involved glomeruli; in these areas moderate increase of the interstitial connective tissue and moderate inflammatory infiltration were also present. The arterioles showed rather pronounced hyaline thickening. Nothing suggested the presence of chronic pyelonephritis. Histologic diagnosis: Severe, nodular Kimmelstiel-Wilson changes and slight, diffuse glomerular hyalinization of the basement membranes.

The histologic changes found in the kidney biopsies from these twelve patients are shown in Table I. The cases have been arranged according to increasing severity of lesions, greatest importance being attached to the glomerular changes. It appears from the table that *diffuse* glomerular changes in the form of hyalinization of the basement membranes were found in all cases (with the exception of two: Case 1 in which the renal symptoms proved to be due to cardiac failure, and Case 12 in which a detailed estimate of the glomeruli could not be made as they had all become completely hyalinized and showed evidences of nodule formation). In six patients (Cases 2 to 7) the glomerular changes were *exclusively* diffuse; in four (Cases 8 to 11) they were both diffuse and nodular, and in only two of these four patients were the nodular changes more pronounced than the diffuse. *Solely nodular changes were thus not demonstrated in this series.*

With regard to the other renal changes in the present series of cases it may be mentioned that the degree of tubular atrophy and increase of interstitial connective tissue might well correspond to the number of affected glomeruli, that the degree of vascular change largely corresponded to that of the glomerular lesions, and that the alkaline phosphatase test (Gomori's method) did not give any characteristic result, only a decrease corresponding to the tubular atrophy.

FIG. 5. Kidney biopsy from sixty-four year old woman with diabetes mellitus for about sixteen years (Case 11). Severe nodular and slight, diffuse glomerular changes; three glomeruli are almost completely hyalinized with remnants of nodules. There is considerable tubular atrophy and rather pronounced increase of the interstitial connective tissue. × 145.

A varying degree of interstitial inflammatory infiltration was found in eight of the twelve patients but only in one (Case 8) was the diagnosis of chronic pyelonephritis suggested. In the other cases the inflammatory infiltration was less pronounced so that it might well be reactive, corresponding to the atrophic changes in the glomeruli and the tubules.

CLINICAL AND LABORATORY FINDINGS

These findings are shown in Table II. It may be mentioned that the series comprised nine females and three males, chiefly in the old age groups, and that they were all suffering from mild diabetes mellitus (except the patient, Case 2, who was in diabetic coma); that nine of the ten patients in whom this examination could be made had diabetic retinopathy; and that ten had arterial hypertension and eight bacteriuria.

Tests for Discrete Renal Functions. The results of these tests are given in Table III. Summarizing, it may be said that for the most part the renal function tests show about the same general reduction in the glomerular filtration rate, the renal plasma flow and the maximal tubular secretory capacity. The filtration fraction is normal in spite of the fact that most of the patients were hypertensive. We have not been able to confirm the findings of Hogeman[16] who found low filtration fractions in diabetic nephropathy.

Comparison between Kidney Biopsy and the Clinical

and Laboratory Findings (*Table* II). This comparison confirms the well known phenomenon that the nodular form of diabetic nephropathy is chiefly present in elderly female diabetics in whom the diabetes is of long-standing and comparatively mild. When the degree and nature of the glomerular changes are compared with the duration of diabetes, it appears that the slight, diffuse changes (Cases 2 to 5) are present in diabetes of comparatively short duration (in one patient, Case 3, however, diabetes was of eleven years' duration) and that the nodular forms (Cases 8 to 12) are present exclusively in cases of from fourteen to twenty years' standing (in one patient, Case 10, the duration of diabetes could not be ascertained). It is, however, remarkable that two patients (Case 6 and 7), aged sixty-nine and twenty-seven years, respectively, in whom diabetes was of twenty-four and sixteen years' duration, respectively, showed *exclusively diffuse*, severe changes. In one of these (Case 6) autopsy sixteen months after the biopsy showed no typical nodular changes.

TABLE I

Case No.	Sex	Patients	Diffuse Glomerular Changes	Nodular Glomerular Changes	Completely Hyalinized Glomeruli	Tubular Atrophy	Increase in Interstitial Connective Tissue	Vascular Changes	Chronic Interstitial Inflammatory Changes	Alkaline Phosphatase Activity	Severity of Pathologic Renal Changes	Inulin Clearance (cc./min.)	Tm_{PAH} (mg./min.)
1	M	E. M.	0	0	0	0	0	?	0	?	0	-	-
2	M	N.R	(+)	0	0	0	0	0	0	+	(+)	Diabetic coma, anuria	
3	F	A.P	(+)	0	(+)	(+)	(+)	?	(+)	?	(+)	91	-
4	F	H.M.	+	0	0	0	0	(+)	0	+	+	88	52.7
5	F	R. J.	+	0	(+)	(+)	(+)	(+)	0	+	+	108	57.4
6	M	J. H.	++	0	++	+	+	++	(+)	(+)	++	26	17.7
7	F	L. L.	++	0	+	++	++	++	+	(+)	++	56	33.1
8	F	B. P.	+	(+)	0	(+)	(+)	?	(+)	+	+	50	28.0
9	F	K. J.	+	(+)	+	+	(+)	+	+	+	+	67	24.7
10	F	S. N.	(+)	++	(+)	+	+	++	(+)	+	++	57	27.7
11	F	A. J.	(+)	++	++	+	(+)	+	(+)	(+)	++	15	5.9
12	F	M. N.	?	+++	+++	+++	+++	++	+	(+)	+++	1	0.11

Thus it seems as if certain cases continue to show only diffuse changes for a very long time whereas others, presumably representing the great majority of cases, must be assumed to go on from the purely diffuse to the nodular-diffuse form. Transition forms of the type shown in Figure 3 and the constant (?) occurrence of diffuse changes together with the nodular ones seem to support the theory that nodular changes develop from the diffuse type of involvement.

With regard to proteinuria, the patients with the slight, diffuse changes had little or no pro-

teinuria, the two patients (Cases 6 and 7) with pronounced diffuse changes had severe proteinuria, and those with nodular changes had moderate to severe proteinuria. The patients with moderate to severe proteinuria had a lowered serum albumin and, in the nodular cases, a strikingly high serum globulin (between 4.0 and 5.3 per cent). Renal edema was present in only three patients (Cases 9 to 11), all nodular cases.

TABLE II

Case No.	Patients	Age, Sex	Duration of Diabetes (yr.)	Earlier Diabetic Coma	Dose of Insulin (cc.)	Proteinuria (g/24 hr.)	Edema	Congestive Heart Failure	Serum Protein (%)	Serum Albumin (%)	Serum Globulin (%)	Diabetic Retinopathy	Arterial Hypertension	Hemoglobin (%)	Blood Urea (mg.%)	Hematuria	Cylindruria	Pyuria	Bacteriuria	Kidney Biopsy: Diffuse (D) and Nodular (N) Glomerular Changes
1	E.M.	59, M	3	0	0.6	9.6–2.5	+++	+	4.6	1.2	3.4	+	+	70	42	0	+	+	0	0
2	N.R.	45, M	0.5	+	0	Anuria	0	+	-	-	-	?	0	?	90	?	?	?	?	(+) D
3	A.P.	56, F	11	(+)	1.0–0.8	+	0	0	7.8	3.9	3.9	+	+	89–76	20	0	0	++	+	(+) D
4	H.M.	63, F	5	(+)	0.3	0	0	0	7.2	3.7	3.5	+	+	100–85	24	0	0	0–+	0	+ D
5	R.J.	42, F	0.5	0	0	0	0	0	7.0	3.8	3.2	0	0	89–74	32	0	0	0	+	+ D
6	J.H.	69, M	24	0	0	3.7–6.2	0	0	6.4	3.5	2.9	+	+	77	41	+	+	+	+	++ D
7	L.L.	27, F	16	0	0.9	4.4–5.6	0	0	6.0	2.9	3.1	+	+	90	61	0	+	+	+	++ D
8	B.P.	65, F	20	0	0.8	1.4	0	0	7.4	2.1	5.3	+	+	81	47	+	0	+	+	+ D/N
9	K.J.	62, F	14	0	0.9–0.4	0.3–0	+	0	6.8	2.6	4.2	+	+	86	33	0	0	+	+	+ D/N
10	S.N.	62, F	?	0	0	1.1–5.8	(+)	0	6.2	2.2	4.0	+	+	85–77	38	+	+	+	+	++ D/N
11	A.J.	64, F	16	+	0.8	1.6–2.7	+	+	6.5	2.4	4.1	?	+	69	115	+	0	+	0	++ D/N
12	M.N.	38, F	18	+	0.5	1.9–4.3	+	0	6.6	2.3	4.3	+	+	60	298	0	0	+	+	+++ N

Diabetic retinopathy was found in nine of the ten patients in whom this examination could be made. It is remarkable that besides being present in all patients with nodular changes, diabetic retinopathy was also found in all of the patients with diffuse changes except one.

In eight of the patients bacteriuria was found at the time when the kidney biopsy was done but only in one of these patients did the biopsy support the diagnosis of chronic pyelonephritis (Case 8).

Case 1 illustrates the difficulty in distinguishing cardiac failure with severe cardiac edema, proteinuria and reduced renal function from the nephrotic syndrome; this patient was known to be suffering from heart disease (with auricular fibrillation) with cardiac failure but the pronounced proteinuria and the low total protein and serum albumin concentrations might suggest the simultaneous presence of diabetic nephropathy. However, kidney biopsy showed completely normal renal tissue and the clinical course confirmed that this was a case of pure cardiac failure with proteinuria and reduced renal function, since treatment with digitalis and confinement to bed completely obviated the edema and the proteinuria, with a great rise of the serum albumin concentration and im-

provement in renal function as measured by the twenty-four-hour endogenous creatinine clearance.

Comparison between Kidney Biopsy Findings and the Results of the Discrete Renal Function Tests (Table III). Comparison of the glomerular filtration rate (inulin clearance) with tubular function (Tm_{PAH}) apparently shows that patients with the nodular form of diabetic nephropathy have a glomerular filtration rate which is relatively better maintained than the tubular secretory capacity; this manifests itself in a higher inulin clearance/Tm_{PAH} ratio in these patients than in those with diffuse glomerular changes (1.78 to 2.72 as compared to 1.32 to 1.88). Case 12 in which the inulin clearance/Tm_{PAH} ratio was 9.1 has been left out of consideration here, as the very low value of Tm_{PAH} (0.11 mg./min.) may, of course, cause large errors in making this calculation.

In addition to examining the relative changes in the discrete functions of the kidney we have also compared the renal functions as a whole with the degree of pathologic changes as a whole. (Table I.) As was to be expected there was, for the most part, a certain parallelism. It may, however, be mentioned that Cases 3, 4 and 5 had almost normal renal function even though the kidney biopsy findings showed moderate hyaline glomerular changes. In Cases 7, 8 and 10 renal function was only moderately reduced in spite of pronounced glomerular changes. It is peculiar that the glomerular filtration rate was so relatively well preserved in several cases in spite of widespread changes in the glomeruli. It seems as if glomeruli with rather pronounced Kimmelstiel-Wilson changes must possess an appreciably greater filtration capacity than would be expected according to the histologic changes, provided the biopsies dealt with here may be considered representative.

COMMENTS

The renal function tests in the present series of cases have largely confirmed the reports of previous authors[11,15,25] concerning a proportionate reduction in discrete functions in diabetic nephropathy. The discrete renal function tests have thus apparently neither afforded any essentially new information nor do they alone increase the diagnostic possibilities in diabetic nephropathy.

The role of the kidney biopsy method in respect to diagnosis may be discussed on the basis of the data assembled in Table IV in which the clinical diagnoses made before biopsy are compared with the biopsy findings. In six cases the clinical diagnosis was intercapillary glomerulosclerosis; in one of these patients (Case 1) the biopsy showed normal renal tissue and the further course of the disease showed that heart failure alone could explain the clinical picture simulating the nephrotic syndrome; in four of these six patients the biopsy showed typical nodular and diffuse changes while in the fifth case exclusively severe diffuse changes were present. In four cases in which the diagnosis diabetic nephropathy had not been made clinically the biopsy showed slight, diffuse changes in three and moderate nodular and diffuse changes in one (Case 9).

Thus in the present series the kidney biopsy method in one case corrected a wrong diagnosis, and in the other instances afforded further information about the nature of the glomerular changes (whether diffuse or nodular-diffuse). More precise diagnosis may presumably have certain prognostic importance.

A diagnostic problem of frequent occurrence is whether or not a diabetic has chronic pyelonephritis. It is well known that chronic pyelonephritis occurs often in diabetes mellitus, and, as is known, the diagnosis is established, *inter alia*, by the presence of pyuria and bacteriuria. However, these two findings are so frequent, especially in elderly women, that their diagnostic value as criteria of the diagnosis of chronic pyelonephritis is often questioned, especially in diabetics in whom other renal disorders, in particular intercapillary glomerulosclerosis, may explain the other signs of disease of the kidney (proteinuria and reduced renal function).

Table IV shows that we have clinically established the diagnosis of chronic pyelonephritis with varying certainty in many cases (Cases 3, 5, 6, 8, 9, 10, 11 and 12), and that bacteriuria was present in eight of the patients at the time of the kidney biopsy. Only in one of these patients (Case 8) did the kidney biopsy support the diagnosis of chronic pyelonephritis. Whether the kidney biopsy method as a diagnostic aid fails in this respect, owing to the focal nature of chronic pyelonephritis, or whether these patients really did not have pyelonephritis but only an infection of the urinary tract of a different nature, cannot now be stated.

The kidney biopsy method can thus be considered a valuable diagnostic aid to verify or exclude the possibility of diabetic nephropathy.

It offers a means by which the nature of the nephropathy can be verified, whether diffuse or nodular-diffuse. Only in exceptional cases, however, will it be of value in the differential diagnosis of chronic pyelonephritis.

It is, however, especially for purposes of investigation that the kidney biopsy method may become of importance; in diabetic nephropathy serial biopsies, histochemical examinations, etc., may presumably afford information

TABLE III

Case No.	Sex	Patients	Inulin Clearance (cc./min.)	Endogenous Creatinine Clearance (cc./min.)	Urea Clearance (cc./min.)	PAH Clearance (cc./min.)	Tm_{PAH} (mg./min.)	Filtration Fraction X 100	Inulin Clearance/Tm_{PAH}	PAH Clearance/Tm_{PAH}	Blood Urea (mg.%)	Kidney Biopsy: Diffuse and Nodular Glomerular Changes *
1	M	E. M.	_	76	-	-	-	-	-	-	42	0
2	M	N. R.	-	-	-	-	-	-	-	-	90	(+) D
3	F	A.P.	91	79	63	506	-	18.0	-	-	17	(+) D
4	F	H. M.	83	69	48	369	62.7	21.0	1.32	6.7	24	+ D
5	F	R. J.	108	73	35	654	57.4	16.5	1.88	11.4	32	+ D
6	M	J H.	26	36	17	163	17.7	15.7	1.45	9.2	41	++ D
7	F	L.L.	56	41	27	289	33.1	19.3	1.69	8.7	61	++ D
8	F	B. P.	50	52	27	-	28.0	-	1.78	-	47	+ D/N
9	F	K. J.	67	72	53	335	24.7	20.1	2.72	13.6	33	+ D/N
10	F	S. N.	57	63	38	262	27.7	21.9	2.07	9.5	38	++ D/N
11	F	A. J.	15	19	10	71	5.9	20.6	2.51	12.1	115	++ D/N
12	F	M. N.	1	1.4	0.8	-	0.11	-	9.1	-	298	+++ N
Normal values (Brun, Hilden & Raaschou[10])			130 (109–150)	-	-	628 (547–668)	65.6 (51.8–79.0)	20.6 (16.9–24.9)	2.01 (1.45–2.36)	9.5 (8.5–10.6)	-	

* D = diffuse changes; N = nodular changes

as to the course of the disease, its pathogenesis and nature. The present small series of kidney biopsies seems, for instance, to support the supposition that the Kimmelstiel-Wilson abnormality originates in the basement membranes of the glomerular tufts in a diffuse form, and with the clinical and laboratory findings in these cases, and the results of discrete renal function tests.

In six cases the biopsy specimen revealed solely diffuse glomerular changes; in four cases nodular-diffuse changes; and in one case completely hyalinized glomeruli with remnants of nodules; in one case the biopsy showed normal renal tissue in a patient in whom the further course of the disease showed that the renal symptoms must have been due to cardiac failure.

TABLE IV

Case No.	Patients	Clinical Diagnosis		Kidney Biopsy*
		Intercapillary Glomerulosclerosis	Other Kidney Disease	Diffuse and Nodular Glomerular Changes
1	E.M.	+	(Heart failure)	0
2	N.R.	?	(Diabetic coma, anuria)	(+) D
3	A.P.	0	Pyelonephritis	(+) D
4	H.M.	0	0	+ D
5	R.J.	0	Pyelonephritis	+ D
6	J.H.	(+)	Pyelonephritis, hypertrophy of the prostate	++ D
7	L.L.	+	0	++ D
8	B.P.	+	Pyelonephritis	+ D/N (+ chronic pyelonephritis)
9	K.J.	0	Pyelonephritis	+ D/N
10	S.N.	+	(Pyelonephritis)	++ D/N
11	A.J.	+	(Pyelonephritis)	++ D/N
12	M.N.	+	Pyelonephritis	+++ D/N

* D = diffuse changes; N = nodular changes

that the nodular form may be a further development of such diffuse changes.

SUMMARY

Kidney biopsy findings in twelve patients with diabetes mellitus have been compared

The kidney biopsy method made possible correction of clinically misdiagnosed diabetic nephropathy in one case, and in four cases which did not show definite clinical signs of diabetic renal disease it revealed the presence of glomerular changes (diffuse in three cases and nodular-diffuse in one case).

Biopsy of the kidney, therefore, has some diagnostic value in diabetic nephropathy. Its value in the differential diagnosis of chronic pyelonephritis, on the other hand, seems to be very limited.

The present kidney biopsy experience apparently supports the theory that diabetic nephropathy originates as diffuse hyalinization in the basement membranes of the glomerular tufts, and that the nodular changes may be considered a further development of the diffuse form.

The discrete renal function tests, which do not *per se* permit any safe diagnostic conclusions with regard to the degree and nature of diabetic nephropathy, seem to indicate that glomeruli with rather pronounced changes of diabetic origin, at least in some instances, have a higher filtration capacity than might be supposed from the histologic picture.

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Needle Biopsy of the Kidney*

A Report of Five Cases of Multiple Myeloma

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THE recent report of Iversen and Brun[1] describing a method of aspiration biopsy of the kidney led us to apply a modification of this technic to the study of the renal pathology in multiple myeloma. It was our impression that two significant contributions could be made: (1) application and possible simplification of a valuable new clinical procedure, i.e., needle biopsy of the kidney and (2) demonstration of the pathologic alterations occurring in the kidney during the course of multiple myeloma.

An attempt will be made to clarify some of the existing ideas regarding the nature of the "myeloma kidney." Two of the five patients in this series have died and a comparison of the biopsy and postmortem material will be presented.

DESCRIPTION OF TECHNIC

The prothrombin and bleeding times were determined a day or two prior to the contemplated biopsy. The procedure was believed to be contraindicated only in the presence of a definite bleeding tendency, suspected perinephric abscess, hydronephrosis or renal malignancy.

The patient was given 1 ounce of liquorice powder the evening before and an enema on the morning of the planned biopsy. Breakfast was withheld. A small, 0.5 by 0.5 cm., lead marker was affixed with adhesive to the skin of the back overlying the expected anatomic position of the right kidney. A 14 by 17 inch upright, anteroposterior x-ray of the abdomen was taken. In the great majority of cases the renal outline was clearly seen and the relative position of the marker noted. The anticipated biopsy site, ideally at the lateral margin of the lower pole of the kidney, was selected by means of skin localization utilizing the relative position of the lead marker.

The biopsy was carried out at the bedside with the patient in a sitting position. The skin was prepared with one of the usual sterilizing solutions. The skin site and subcutaneous tissues in a direct anteroposterior line were liberally infiltrated with 1 per cent procaine solution. By means of a 3 inch, 22-gauge needle, an attempt was made to anesthetize the tissues to the anticipated level of the renal capsule. A Vim-Silverman needle was then introduced to the same depth as the infiltration needle, advanced about 3 cm. further, and the biopsy was carried out. The specimens were immediately fixed in 10 per cent formalin solution. All patients were carefully observed during the subsequent eight-hour period and each specimen of urine voided in the ensuing twenty-four hours was examined microscopically.

The technic of anteroposterior and lateral intravenous pyelography for determining the distance from the skin to the posterior surface of the kidney was used by Iversen and Brun.[1] In our hands this method has proven to be no more valuable than the description of localization outlined above. In addition, the single x-ray tended to simplify the necessary preparation.

CASE REPORTS

CASE 1. A fifty-seven year old white male was admitted to the Veterans Administration Hospital, Brooklyn, New York, on December 12, 1951, with a complaint of paralysis of the lower extremities. The diagnosis of multiple myeloma had been made in September, 1951, after he had had low back pain for one year. He had been treated with stilbamidine and urethane prior to admission. On entry to the hospital he was found to have tumefactions of the skull and bilateral supraclavicular masses. A flaccid paralysis and areflexia of the lower extremities were present as well as loss of all sensory modali-

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ties below the level of the tenth thoracic vertebrae. He was incontinent of urine and feces. The white blood count was 3,400 with 80 per cent polymorphonuclear leukocytes and 18 per cent lymphocytes. Serologic test for syphilis was negative as were the serum examinations for the interstitial tissue there was an increase of loose connective tissue. The renal tubules in areas showed a moderate swelling of the cytoplasm, especially the proximal convoluted loops. This cytoplasmic swelling was light pink, granular in appearance and the lumina of the

TABLE I

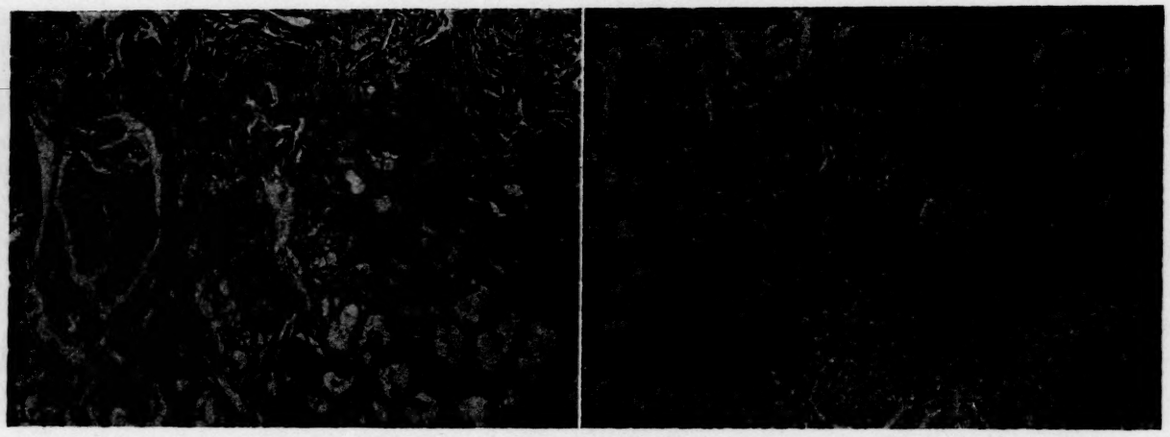
Case	Urine					Peripheral Blood			Serum				
	Specific Gravity	Albumin	Microscopic Examination	Protein (gm./24 hr.)	Bence-Jones Protein	RBC (mil.)	Hgb. (gm. %)	ESR (mm./hr.)	Protein (gm. %)	Albumin (gm. %)	Globulin (gm. %)	Calcium (mg. %)	BUN (mg. %)
I	1.008 1.014	3+	Hyaline casts	1.1	+	3.5	9.0	26	10.3	2.8	7.5	11.0	25.2
II	1.007	2+	Granular casts	2.9	−	2.5	5.8	56	7.0	3.5	3.5	10.0	13.0
III	1.006 1.013	1+	Fine and coarsely granular casts	3.9	+	2.0	5.8	76	11.3	3.1	8.2	12.6	64.0
IV	1.016 1.025	2+	Hyaline and granular casts		−	3.0	9.0	58	12.1	3.3	8.8	16.8	22.3
V	1.004 1.014	2+	Amorphous material	1.6	−	3.7	10.0	56	8.5	2.9	5.6	9.5	30.0

cryoglobulin[2] and Bence-Jones protein.[3] Smears of a bone marrow aspirate revealed 18 per cent myeloma cells (Table I for laboratory data). A retention catheter was placed in the urinary bladder and the patient was treated with urethane and cortisone as well as routine supportive measures. This treatment resulted in subjective improvement with increased appetite and sense of well being. There was, however, little to suggest that the natural course of the disease had been altered. Bleeding time, clotting time, prothrombin time and platelet count were normal. A right renal biopsy was carried out on February 28, 1952. There were no complications from this procedure and transient microscopic hematuria which followed cleared within twenty-four hours. Despite continued therapy his condition became progressively worse and he expired on March 21st, three weeks after the renal biopsy.

The biopsy specimen included a portion of the cortex and a small part of the medulla. (Fig. 1A.) Examination of a section stained with hematoxylin eosin showed that the glomeruli were of average size and the lumina of some of Bowman's space contained small amounts of pink amorphous material. In an occasional glomerulus Bowman's capsule was slightly to moderately thickened by an increase of pink hyaline material. In focal areas within tubules were either completely obliterated by the swelling or greatly narrowed. Lying in the lumina of some of the tubules was pink hyaline material.

Elastica van Gieson stain showed that the focal zones of fibrosis within the interstitial connective tissue and the hyalinized glomeruli took a red stain (connective tissue). The hyaline casts as well as the tubular swelling had a brown appearance. A Congo red stain of the tissue showed no evidence of amyloid deposition within the glomeruli, interstitial tissue or blood vessels. The periodic acid Schiff reaction of the same tissue showed, in addition to the positive reaction seen in the basement membranes of the various structures, an occasional positive reaction in the casts within some of the tubular lumina and the cytoplasm of some of the swollen tubules.

At autopsy the kidney (Fig. 1B) showed a slight to moderate focal increase of interstitial connective tissue with a marked decrease in the number of renal tubules. The glomeruli here were more closely approximated and had a pink hyaline appearance. Others showed a moderate fibrous thickening of Bowman's capsule. Some of the renal tubules in the remaining areas, particularly those of the proximal convoluted loops, were slightly to moderately swollen and their cytoplasm was pink granular in appear-



1A 1B

FIG. 1. Case I. A, biopsy specimen. A small area of increased interstitial fibrosis is present in the cortex. The renal tubules show moderate swelling of the cytoplasm with obliteration of some of the lumina; hematoxylin and eosin stain, × 120. B, autopsy specimen. There is a large area of interstitial fibrosis in the cortex with a close approximation of the glomeruli. There is swelling of the cytoplasm of the tubules and hyaline casts in some of them; hematoxylin and eosin stain, × 75.

ance. Lying in the lumina of some of the tubules were deposits of calcium. The moderate sized blood vessels showed only slight thickening of their walls by an increase of connective tissue within the intimal aspects. The pathologic diagnosis was arterionephrosclerosis, slight.

When the postmortem material was compared with the biopsy specimen, there was very little demonstrated in the former that could not be revealed in the biopsy sections. The only feature not adequately shown was the presence of large focal scars and the changes in the moderate sized blood vessels. In a small section, such as was taken here, the representative changes were for the most part visualized in the biopsy specimens; in fact, the changes in the renal tubules were much better visualized in the biopsy specimen.

CASE II. A sixty-two year old white male was admitted to the V.A. Hospital, Brooklyn, on February 11, 1952, with a complaint of progressive edema of the lower extremities and weakness of six months' duration. He had been treated for congestive heart failure without resolution of symptoms. On admission he was found to be chronically ill with mild dyspnea and marked pallor. Blood pressure was 170/80. The heart was not apparently enlarged. Sinus tachycardia with a grade III apical systolic murmur was noted. The aortic second sound was louder than the pulmonic. The liver edge was felt 2 cm. below the right costal margin. Four plus pitting edema of the lower extremities was present. The white blood count was 11,000 with 55 per cent polymorphonuclear leukocytes, 37 per cent lymphocytes and 3 per cent eosinophils. Serologic test for syphilis was negative as were the serum examinations for cryoglobulin and Bence-Jones protein (see Table I for other laboratory data). Smear of a bone marrow aspirate revealed nests of myeloma cells. Skeletal x-rays revealed an isolated area of radiolucency in the left humerus. Bleeding time, clotting time, prothrombin time and platelet count were normal. A right renal biopsy was done on February 27th. There were no complications attending this procedure and urine examinations failed to reveal any hematuria. The patient was treated with a low salt diet, mercurial diuretics and repeated small transfusions of packed red blood cells. On March 21st the patient was discharged from the hospital in an asymptomatic state.

Hematoxylin eosin stain of the biopsy specimen showed a portion of the cortex and a small portion of the medulla with an occasional pink hyaline glomerulus. (Fig. 2.) The tubular cytoplasm of a moderate number of renal tubules within the cortex showed extensive swelling, some containing irregular vacuoles. The lumina of some tubules showed a pink amorphous material within them; others contained calcium. In areas within the cortex there was a focal increase of interstitial connective tissue. Branches of the small arteries showed a slight to moderate fibrous thickening of the intima.

An elastica van Gieson stain showed some of the casts in the lumina of the tubules to have a

FIG. 2. Case II. Biopsy specimen. The tubules show moderate to extensive swelling of the cytoplasm with obliteration of some of the lumina. There is one intact and one obliterated glomerulus; hematoxylin and eosin stain, × 120.

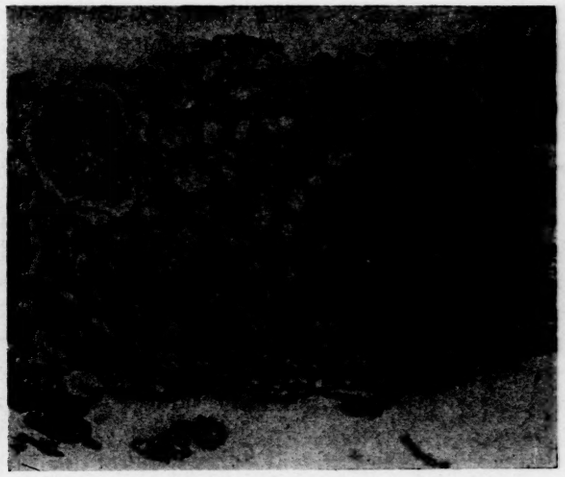


FIG. 3. Case III. Biopsy specimen. The cytoplasm of some of the tubules is moderately swollen and vacuolated. An occasional hyaline cast is present; hematoxylin and eosin stain, × 120.

light yellow appearance. A Congo red stain failed to reveal any evidence of amyloid either within the glomeruli, the interstitial tissue or the blood vessels. A periodic acid Schiff stain of the tissue showed a positive reaction of the basement membranes of the renal tubules, the glomeruli and Bowman's capsule. Small areas within the lumina of tubules as well as some of the hyaline casts described with the hematoxylin eosin stain also gave a positive reaction.

The changes described within this kidney were those of tubular swelling, chiefly within the proximal convoluted loops. There was obliteration of many of the lumina as a result of this swelling. There was also a slight increase in interstitial connective tissue and a moderate number of hyaline casts within the lumina of the tubules.

CASE III. A fifty-nine year old white male was admitted to the V.A. Hospital, Brooklyn, N. Y., on January 11, 1952, with a complaint of weakness and back pain for four weeks. In March, 1951, following a pathologic fracture of the right humerus, a bone marrow examination was carried out and a diagnosis of multiple myeloma made. He received six transfusions of whole blood at that time. On admission he was found to be chronically ill with marked pallor. The blood pressure was 155/100. There was bone tenderness over the lumbar spine and upper extremities. The white blood count was 4,000 with 64 per cent polymorphonuclear leukocytes, 34 per cent lymphocytes and 2 per cent monocytes. Serologic test for syphilis was negative as were serum examinations for cryoglobulin and Bence-Jones protein (see Table I for other laboratory data). A smear of bone marrow revealed extensive myelomatous infiltration. Skeletal x-rays revealed the presence of multiple and diffuse osteolytic lesions. A persistent anemia necessitated repeated whole blood transfusions. The administration of urethane and cortisone resulted in marked symptomatic improvement with relief of pain, increased appetite and a sense of well being. The course of the disease was not apparently altered by this treatment. Bleeding time, clotting time, prothrombin time and platelet count were normal. A right renal biopsy was done on February 27, 1952. There were no complications attending this procedure and a transient microscopic hematuria cleared in less than twenty-four hours. Despite the continued administration of the above mentioned drugs, as well as general supportive measures, his condition progressively deteriorated and he expired on April 16, 1952, seven weeks after the renal biopsy. Permission for postmortem examination was denied.

Hematoxylin eosin stain of the biopsy specimen showed a portion of kidney which included both the cortex and medulla. (Fig. 3.) The glomeruli were present in their usual numbers. The basement membrane of an occasional glomerulus was slightly thickened by an increase of connective tissue. The renal tubules showed a moderate swelling of the cytoplasm, vacuolated in some regions. Lying in the lumen of an

occasional tubule was a pink homogeneous material. Present in an occasional tubule, particularly in those within the lower portion of the medulla, were pink amorphous casts as well as calcium. The moderate sized renal arteries showed a slight fibrous thickening of the intima.

An elastica van Gieson stain showed an occasional glomerulus to be occupied by a red zone (connective tissue). The blood vessels within the tissue showed a slight thickening of the intimal aspects by an increase of connective tissue. A Congo red stain failed to reveal any evidence of amyloid deposition within the glomeruli, the blood vessels or the interstitial tissue. The periodic acid Schiff reaction of this tissue showed many of the casts within the medulla to have a positive reaction. The pink amorphous material lying within the lumina of the tubules, particularly within the cortex, for the most part did not give a positive Schiff reaction.

The changes present within this kidney were those of a slight increase of interstitial fibrosis, more advanced in the cortex than in the medulla. Hyaline casts were present within the lumina of the tubules, particularly in the medulla. These for the most part gave a positive Schiff reaction. The blood vessels showed only a slight fibrous thickening of the intima.

Case IV. A sixty year old white male was admitted to the V.A. Hospital, Brooklyn, on January 4, 1952, with a complaint of low back pain for three months. He was perfectly well until five months prior to admission when he developed symptoms of progressive weakness and anorexia. This was followed by a steadily increasing, non-radiating, low back pain for which he was finally hospitalized. He was found to be chronically ill with marked pallor. The blood pressure was 180/100. There was weakness of the left lower extremity although reflexes and all sensory modalities were normal. The white blood count was 6,800 with 49 per cent polymorphonuclear leukocytes, 50 per cent lymphocytes, and 1 per cent monocytes. Serologic test for syphilis was negative as were serum examinations for cryoglobulin and Bence-Jones protein (see Table I for other laboratory data). Skeletal x-rays revealed multiple osteolytic lesions, particularly in the thoracolumbar spine and skull. A smear of bone marrow revealed the presence of 12.5 per cent myeloma cells. The administration of urethane resulted in marked relief of pain. Whole blood transfusions were given. Bleeding time, clotting time, prothrombin time and platelet count were normal. A right renal biopsy was performed on February 20, 1952. There were no complications; a transient microscopic hematuria cleared within twenty-four hours. The patient was discharged on March 21st.

Hematoxylin eosin stain of the biopsy specimen showed a portion of the cortex and only a small fragment of the medulla. The glomeruli for the most part were large and the capillary loops within them were moderately dilated. In an occasional glomerulus there was a moderate fibrous thickening of Bowman's capsule. Within the remaining parenchyma there was, in focal areas, an increase of interstitial connective tissue. At the periphery of the focal areas of fibrosis the renal tubules were moderately dilated and lined by flattened epithelial cells. In the remaining portion of the cortex many of the proximal convoluted tubules showed moderate to extensive swelling of the cytoplasm of the cells with obliteration of many of the tubular lumina. Lying in the lumina of other tubules were collections of pink homogeneous material. Branches of the moderate sized renal arteries showed moderate intimal thickening by connective tissue. The casts within the lumina of the tubules had a light pink appearance with elastica van Gieson stain. Congo red stain failed to reveal the presence of amyloid deposition in either the blood vessels, glomeruli or interstitial tissue. A periodic acid Schiff reaction showed, in addition to the positive stain of the basement membranes of the glomeruli, Bowman's capsule, and renal tubules, a positive reaction in some of the casts.

This case showed areas of focal fibrosis within the cortex. There was not enough renal parenchyma present to state whether this was due to chronic pyelonephritis or arterionephrosclerosis. It is possible that both lesions were present. The tubular swelling, particularly that of the proximal convoluted tubules, was of a moderate to advanced degree but did not give a positive Schiff reaction. In the lumina of the tubules only a few of the hyaline casts gave a positive Schiff reaction.

Case V. A seventy-nine year old white male was admitted to the V.A. Hospital, Brooklyn, on February 18, 1952, with a complaint of low back pain of one and one-half years' duration. Following a pathologic fracture of the right

humerus in October, 1951, the diagnosis of multiple myeloma had been made. Despite treatment with urethane and stilbamidine he experienced increasing back pain and marked weight loss. Hospitalization was advised. On admission he was found to be chronically ill, cachectic, with marked pallor. The blood pressure was 140/60. There was marked thoracic scoliosis with considerable tenderness over the lumbar spine. The white blood count was 7,200 with 85 per cent polymorphonuclear leukocytes and 15 per cent lymphocytes. Serologic test for syphilis was negative as were serum examinations for cryoglobulin and Bence-Jones protein (see Table 1 for other laboratory data). A smear of bone marrow revealed massive infiltration of myeloma cells. Skeletal x-rays revealed multiple and diffuse osteolytic lesions. Bleeding time, clotting time, prothrombin time and platelet count were normal. A right renal biopsy was carried out on March 3, 1952. There were no complications; transient microscopic hematuria cleared in twenty-four hours. Despite the continuance of general supportive measures his condition slowly deteriorated and he expired on March 21st, eighteen days after the renal biopsy. Permission for postmortem examination was obtained.

Hematoxylin eosin stain (Fig. 4) of the biopsy specimen showed a portion of the cortex and only a small part of the medulla. The glomeruli were of average size. Lying in some of Bowman's spaces was a pink homogeneous material. In small focal areas within the cortex there was a slight increase of interstitial connective tissue. Lying in the lumina of some of the renal tubules was a pink hyaline material. The proximal convoluted tubules in many areas were slightly to extensively enlarged by a pink granular swelling of their cytoplasm. Small branches of the arteries and arterioles showed moderate thickening of their walls at the intima with a narrowing of the lumina.

An elastica van Gieson stain showed an occasional glomerulus to be occupied by concentrically arranged red material (connective tissue). In focal areas within the interstitial zones there was a slight increase of connective tissue. Congo red stain showed no evidence of amyloid deposition either in the blood vessels, glomeruli or interstitial tissue. A periodic acid Schiff stain revealed the positive reaction in the basement membranes of the blood vessels, glomeruli and Bowman's capsule. There was also a positive

FIG. 4. Case v. Biopsy specimen. The glomeruli are intact. There is moderate swelling of the epithelium with obliteration of some of the tubular lumina. An occasional tubule contains a hyaline cast; hematoxylin and eosin stain, × 120.

reaction in an occasional cast lying within the lumen of the tubules. In an occasional region there was also a positive reaction in the cytoplasm of some of the swollen tubules. In some regions the positive Schiff material within the lumen of the renal tubule was directly continuous with that in the cytoplasm of the cell.

There was evidence in this case of arterio- and arteriolarnephrosclerosis. There was tubular swelling, chiefly within the proximal convoluted tubules, and hyaline casts were present within the lumina. Only a few of the casts and a rare area of the tubular cytoplasm gave a positive Schiff reaction.

The kidney at autopsy showed occasional superficial depressions on the surface. Within the cortex and corresponding to these depressions there was a moderate increase of interstitial connective tissue. In these regions there was a decrease in the number of renal tubules and those which remained were compressed. Here there was a close approximation of the glomeruli, some of which had a pink hyaline appearance. Other glomeruli showed moderate thickening of Bowman's capsule as the result of an increase of connective tissue. The moderate sized renal arteries showed moderate and irregular intimal thickening by loose connective tissue. The arterioles showed a moderate thickening by pink hyaline material. The renal tubules, particularly the proximal convoluted tubules, were moderately swollen and their cytoplasm was light pink granular in appearance, the lumina of many of these tubules being

either obliterated or greatly narrowed. Calcium was present within the lumen of an occasional tubule, especially in the medulla. The pathologic diagnosis was arterio- and arteriolarnephrosclerosis, moderate.

It is worth noting that the arterio- and arteriolarsclerosis were discernible in the biopsy sections although the extent of involvement was, of course, much better visualized in the autopsy specimen. The large scars seen in the autopsy kidney, for example, were not at all visualized in the biopsy slide. One could imagine that if one of the depressed scars were aspirated, the tubular changes in the intact portion of the kidney would be entirely missed. The tubular changes, on the other hand, were seen as well in the biopsy slide as in the autopsy material.

COMMENTS

Despite the fact that considerable disagreement exists regarding the pathogenesis of renal insufficiency when it occurs in multiple myeloma, it is well accepted that alteration in renal function is manifested by a low or fixed specific gravity of the urine with loss of concentrating power, and by albuminuria, nitrogen retention and secondary anemia.[4] Bence-Jones proteinuria may be present. Other signs which frequently accompany chronic renal disease, such as edema, hematuria, hypertension and retinitis, are usually absent in the renal insufficiency associated with multiple myeloma.[5] It has been demonstrated that the glomerular filtration rate is impaired to an equal or greater extent than the tubular excretory capacity. The filtration fraction is not consistently altered. These findings suggest that glomerular as well as tubular changes occur but the absence of a consistent fall in filtration fraction argues against a primary or predominant glomerular lesion.[6]

All of the cases in the present series were found to be anemic and all had albuminuria, of varying degree. On repeated examinations Bence-Jones protein was found in the urine of only two patients. There was an alteration of the specific gravity of the urine in four cases. Abnormal urinary sediment was present in four cases and in three a significant degree of nitrogen retention was persistently found. Every case had x-ray evidence of myelomatous involvement as evidenced by single, multiple and/or diffuse osteolytic lesions. With the exception of Case II, whose disease was considered to be in an early phase, the patients had striking complaints of bone pain.

We believe that the amount of renal parenchyma removed by biopsy is adequate to study the tubular changes and that these changes are representative of the remaining tissue. This is well demonstrated in the two cases in which autopsies were performed subsequent to needle biopsy. Examination of the kidney in this manner, however, may not reflect the true picture of other renal disturbances, such as chronic pyelonephritis or arterionephrosclerosis.

The changes in the renal tubules in these cases were characterized by a slight to moderate swelling of the renal tubules which in an occasional zone gave a positive Schiff reaction. All five kidney biopsies showed the presence of protein precipitate and hyaline casts in the tubular lumens, only a few of which gave a positive periodic acid Schiff reaction. We did not observe Bence-Jones protein deposits in the cytoplasm of the tubules in the two cases showing this substance in the urine. Casts and calcium were found in the tubular lumens and in areas of interstitial fibrosis but we cannot consider these to be characteristic of multiple myeloma. The foci of interstitial fibrosis were at sites different from the zones containing the casts and were not a reaction to the latter. Another feature of this material is that it did not appear to be more extensive or different from many other kidneys which we have examined in which no multiple myeloma was present. Congo red stains of the cases herein reported showed no evidence of amyloid deposition in the tissues.

Opinion is divided concerning the pathogenesis of renal insufficiency in multiple myeloma. Forbus and Perlzweig[7] state that the excretion of large amounts of Bence-Jones protein over a period of months results in toxic injury to the tubular epithelium and secondarily to obstruction of the kidney tubules by precipitated protein. The precipitated Bence-Jones protein behaves as a foreign body calling forth a reaction characterized by: (1) invasion of interstitial tissues and of the tubules by wandering cells of both polymorphonuclear and mononuclear phagocytic type, (2) formation of large multinucleated syncytial cell masses about the hyaline protein plug and (3) partial or complete removal of the foreign body protein plug by phagocytic activity of the wandering cell. The tubular epithelium which desquamates probably plays no role in the phagocytosis of the

precipitated protein. Holman[8] believes that there is no toxic effect of Bence-Jones protein but that the alterations are due to blockage of the tubules and that this is substantiated by proximal tubular dilatation. The basement membrane was intact. Bannick and Greene[5] believe that the renal insufficiency is the result of chronic tubular degeneration with subsequent fibrosis. They demonstrated diffuse degenerative changes in the tubular epithelium, with the glomeruli only slightly involved. Bell[9] in his review states that casts are the chief cause of renal insufficiency. The atrophy of the tubule is secondary to disuse and not due to primary degeneration. He found casts in seven of eleven cases, in three of which the casts were surrounded by giant cells. It is Bell's thought that the fusion of macrophages which enter the tubule from without form the giant cell. He adds that Bence-Jones protein may be excreted over long periods without renal damage and is not responsible for basement membrane injury. In one case the glomerular capillaries were apparently obstructed by plasma of high protein content. Foord[10] states that renal insufficiency apparently results from plugging of glomerular capillaries by inspissated protein and possibly by the clumping of erythrocytes (rouleaux) or changes in the osmotic pressure due to the increased protein. Gunn and Mahle[11] presented the pathologic picture of one case of megakaryoblastic myeloma. They described numerous dilated tubules which were filled with eosinophilic hyaline masses, many of which were in the form of rhomboid crystals. In places where the tubular epithelium had disintegrated the crystalline masses were partly surrounded by multinucleated giant cells and the glomerular alterations were slight, consisting of a thickening of Bowman's capsule, occasional adhesions between capsule and tuft, or general atrophy of the glomerulus. The small and medium sized arteries were much thickened and the lumina were often reduced or completely obliterated. They believe the crystals represent a specific myelomatous change. Thannhauser and Breiton[12] refer to three renal changes in myeloma: massive tubular blockage, amyloid of the kidney and chronic nephritis. Oliver[13] comments on the extensive tubular blockage by protein material and indicates that "in certain cases the proximal convolution is also distended and filled with the coagulated protein." Batts[14] concludes that the renal findings in myeloma are not characteristic and that there is no correlation between severity of renal damage and Bence-Jones protein in the urine. Armstrong[6] further suggests the possibility of considerable cast formation developing only as a terminal event related to precipitation of Bence-Jones protein due to dehydration and acidosis.

It is our belief, however, that no definitive answer to these problems is available. The results of this work would suggest that there are no pathologic features, as demonstrated by biopsy specimen, which could be considered pathognomonic for multiple myeloma. The renal lesions demonstrated by biopsy and adequately confirmed in two postmortem specimens were no more extensive or greatly different from those frequently seen in both biopsy and postmortem material in conditions other than multiple myeloma. The similar appearance of tubular swelling and protein precipitate in the biopsy and postmortem sections would suggest that these features are not caused by an agonal anoxia, shock or postmortem changes in the tissue but rather reflect the pathologic alterations existing in the given case.

SUMMARY

1. A simplified technic for Vim-Silverman needle biopsy of the kidney is presented. This procedure was performed in five cases of multiple myeloma. There were no complications except for transient microscopic hematuria.

2. The material obtained by biopsy was adequate for diagnosis and was comparable to the postmortem material obtained in two cases. A biopsy specimen adequately demonstrates parenchymal lesions of a diffuse nature.

3. Hematoxylin eosin, elastica van Gieson, Congo red and periodic acid Schiff stains were used on all material. No pathologic findings were demonstrated that could be considered specific for multiple myeloma.

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Needle Biopsy of the Liver*

IV. Relationship of Clinical and Laboratory Findings to Histologic Structure in 100 Cases of Portal Cirrhosis

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It has been shown that a specimen of liver tissue obtained by needle biopsy usually reflects the over-all histologic picture in diffuse liver disease, including hepatic cirrhosis.[1–6] A number of reports indicate a general correlation between the pathologic findings in such biopsy specimens and clinical or laboratory observations;[4,7–15] while other studies have pointed out a lack of such a relationship.[2,16–19] To throw additional light on this problem an analysis was made of 100 cases of cirrhosis of the liver seen at the Gastric Laboratory of the Cincinnati General Hospital in which needle biopsy of the liver was performed. Common clinical and laboratory observations were analyzed in relation to the degree of fibrosis and the amount of progressive activity observed in the biopsy specimens.

METHODS AND MATERIALS

The technic of liver biopsy as performed at the Cincinnati General Hospital has been previously described.[20] The material comprising this study was culled from 156 cases of cirrhosis. Thirty-seven cases were excluded because of inadequate clinical, laboratory or biopsy material and nineteen cases of biliary cirrhosis were eliminated because of the complicating features of infection or obstruction. The remaining 100 cases included in this study are represented by a total of 123 biopsy specimens. From a histologic point of view they are all classified as portal cirrhosis.

There were sixty-seven males and thirty-three females in the series. The ages ranged from seventeen to seventy-eight years, with the majority of patients between thirty-one and sixty at the time of biopsy. Twenty-one of the patients were Negro (eleven male and ten female).

The clinical features evaluated were: (1) hepatic decompensation, which was assumed to exist when ascites, edema (in the absence of cardiac disease) or jaundice was present; (2) vascular spiders; (3) esophageal varices (demonstrated by roentgen studies and/or esophagoscopy).

The laboratory tests used were: (1) total serum protein (modification of the method of Wolfson et al.;[21] lower level of normal 6 gm. per cent); (2) serum albumin[21] (lower limits of normal 4 gm. per cent); (3) thymol turbidity (method of Maclagan at a pH of 7.55 as modified by Shank and Hoagland;[22,23] readings over 6 units are considered abnormal in this laboratory); (4) cephalin-cholesterol flocculation (method of Hanger;[24] flocculation of 2 plus or more in twenty-four hours considered abnormal); (5) total serum bilirubin (method of Ducci and Watson[25] with 1.2 mg. per cent taken as the maximum level of normal); (6) bromsulphalein retention (5 mg./kg.-forty-five-minute determination, as suggested by Mateer et al.[26] with 6 per cent retention as the upper limit of normal). With few exceptions all of the biochemical determinations were made in the Gastric Laboratory of the Cincinnati General Hospital and were carried out within three days of the procurement of the biopsy specimen. Not every laboratory test was performed on every patient.

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PATHOLOGIC CRITERIA

The needle biopsy specimens were all formalin-fixed, sectioned in paraffin and stained with hematoxylin and eosin. In addition, many were stained with Masson's trichrome or the van Gieson connective tissue stains in order to indicate more clearly the amount of fibrosis.

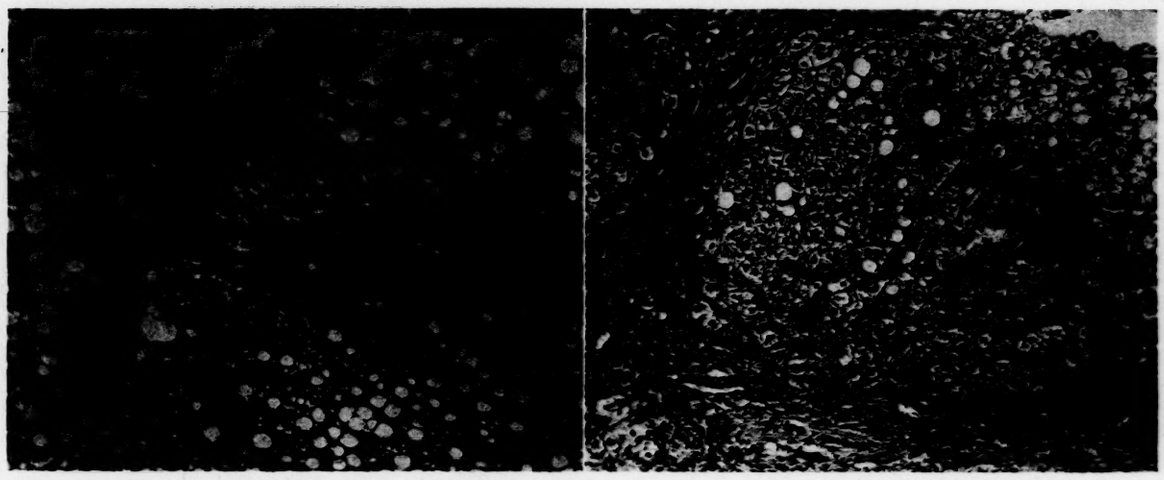
Portal cirrhosis is characterized by diffuse nodular hepatic disease with fibrosis resulting from parenchymatous destruction of varied cause and with subsequent regeneration and fibrous repair. Specifically excluded from this series are those forms of disease resulting from obstruction, pyogenic infection, parasitism, syphilis and hemochromatosis. In general, an attempt was made to distinguish two forms of portal cirrhosis; the post-necrotic (post-hepatitic) variety of which thirty-one examples were identified, and the nutritional type (alcoholic or Laennec) of which there were forty-six examples. In twenty-three instances the microscopic findings did not lend themselves to such subdivision and these were listed simply as portal cirrhosis.

In all specimens there were evidences of architectural distortion with fibrosis and inflammation of varying intensity and parenchymatous alterations consistent with either cellular degeneration or regeneration or both.

Nutritional cirrhosis was characterized almost invariably by coarse fatty vacuolization of hepatic parenchyma. Generally abundant, the lipid appeared as large vacuoles within cells and in more severe processes as pools of lipid, extracellular in location, surrounded by the viable nucleated remnants of cells from which it had been disgorged. It was not possible to determine a predilective site in the lobule since pseudolobulation was the rule in these cases. In addition to lipid other manifestations of disturbed cellular function were occasionally identified by the demonstration of hyaline bodies ("alcoholic hyaline," "F. B. Mallory bodies") within the cytoplasm. In the more actively progressive lesions foci of individual cell necrosis were characterized by nuclear pyknosis, cytoplasmic coagulation, or cytolysis. About these foci appeared reactive leukocytes in small numbers, neutrophiles in most and lymphocytes in some. The portal islets were invariably enlarged as the result of perceptibly increased fibrous tissue. Accompanying this was an inconstant lymphocytic infiltration and relatively scant evidence of bile duct proliferation. Projecting from the islets were delicate tongues of fibrous tissue. These occasionally reached adjacent islets, and also extended into lobules where they appeared to be joined by similar processes emerging from the vicinity of central veins. We have termed this process "creeping fibrosis," implying thus a slowly progressive character. The result of this lesion was to produce both encapsulation and segmentation of the lobules (pseudolobulation) and ultimately the characteristic micronodular structure of this form of cirrhosis. Often seen within the fibrous tongues were venous channels and lymphocytes, less frequently twigs of biliary ductules or arterioles. Bile duct reduplication was usually not a very prominent picture in this group of specimens. In the advanced lesion micronodular pseudolobules (1 to 2 mm. in diameter) usually lacking central veins were seen. The trabeculae generally remained comparatively narrow, rarely attaining the width seen in post-necrotic cirrhosis.

Post-necrotic cirrhosis probably results from the effect of a number of hepatotoxic agents. The cirrhosis that supervenes with repair of such lesions is characterized by the presence of broad fibrous bands of coarse collagen often containing considerable numbers of bile ductules and greater or lesser amounts of lymphocytic inflammatory exudate. Of note is the fact that inflammation of this character when present is universally distributed throughout the trabecular framework. Since the essence of the lesion is multi-lobular destruction, the portal areas as entities are lost. With dissolution of multiple lobules there is coalescence of the stromal and portal components. Regeneration from persisting lobules or groups of cells results in nodulations of variable caliber ranging from a fraction of a millimeter up to several centimeters in diameter. This is in contradistinction to the relatively uniform fine nodularity seen in nutritional cirrhosis. Since "creeping fibrosis" is not a significant factor in this form of disease, central veins often persist; indeed in many nodules two or more venous channels may appear although they are rarely centrally located.

Fat within cells is uncommon and, when present, the small amounts rarely form extracellular pools. In the specimens which are the seat of progression individual cells in the process of necrosis are commonly encountered. These are usually shrunken, deeply staining and reveal a reactive satellitosis of lymphocytes. Evidences



1 2

FIG. 1. Mild activity and mild fibrosis in a case of nutritional cirrhosis. Although fat is prominently displayed, the degree of inflammatory reaction and liver cell necrosis is slight; early fibrosis ("creeping fibrosis") is evident; × 165.

FIG. 2. Moderate activity and moderate fibrosis in a case of nutritional cirrhosis. Fibrosis is more severe than in Figure 1 and frank pseudolobulation is now evident. Although there appears to be less fat in the area photographed, there is increased portal inflammation and parenchymal cell necrosis; × 165.

of regeneration are also simultaneously apparent. Such cells are swollen, their nuclei vesicular, multiple or in process of mitosis.

Specimens were classified as portal cirrhosis when clear-cut distinction between the two specific varieties could not be made. In all instances there were varying degrees of portal fibrosis, bile duct reduplication, inflammation and liver cell necrosis. It is believed that in many of these cases one of the basic forms of portal cirrhosis was complicated by the other, not an unusual circumstance.

The degree of cirrhosis was estimated as mild, moderate or severe on the basis of the comparative amount of fibrosis present in relation to viable parenchyma. Activity was also adjudged as mild, moderate or severe, utilizing as criteria the amount of trabecular inflammatory reaction, the persistence of parenchymatous cell necrosis and evidences of liver cell regeneration. An additional criterion utilized in the nutritional group was the amount of fat present. (Figs. 1 to 3.)

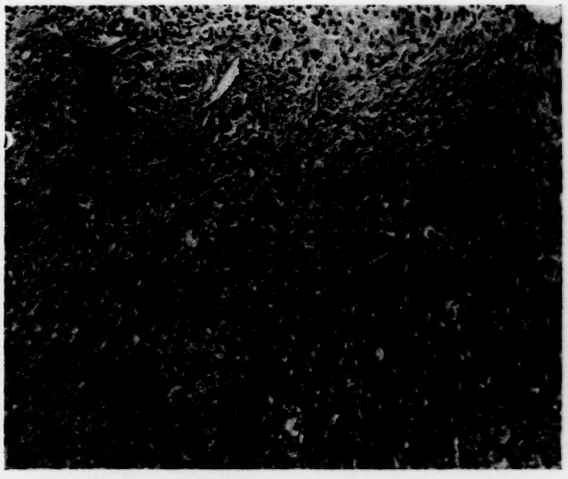


FIG. 3. Mild activity and severe fibrosis in a case of post-necrotic cirrhosis. A broad fibrous strand courses through the photograph producing distortion of lobular structure. Inflammation is mild and there is little liver cell necrosis; × 165.

RESULTS AND OBSERVATIONS

Activity

1. *Hepatic Decompensation.* The presence or absence of jaundice, edema or ascites was noted 119 times in conjunction with 123 specimens. In ninety-one instances (76 per cent) the patient was considered to be decompensated. Figure 4 shows that thirty-six (77 per cent) of forty-seven biopsies showing slight activity were associated with evidence of decompensation as were thirty-eight (70 per cent) of fifty-four with moderate activity and seventeen (94 per cent) of eighteen with marked activity. From these data an inconsistent relationship between activity and decompensation is noted.

2. *Esophageal Varices.* Esophageal varices were

demonstrated in twelve (18 per cent) of sixty-five instances in which they were sought. Figure 4 demonstrates the relationship between activity of disease and the occurrence of varices. Two (9 per cent) of twenty-three specimens showing mild activity were associated with varices as were seven (22 per cent) of thirty-two instances with moderate activity and three (33 per cent) of ten specimens with marked activity. These data suggest that demonstrable varices occur more frequently in the moderately and markedly active phases of cirrhosis.

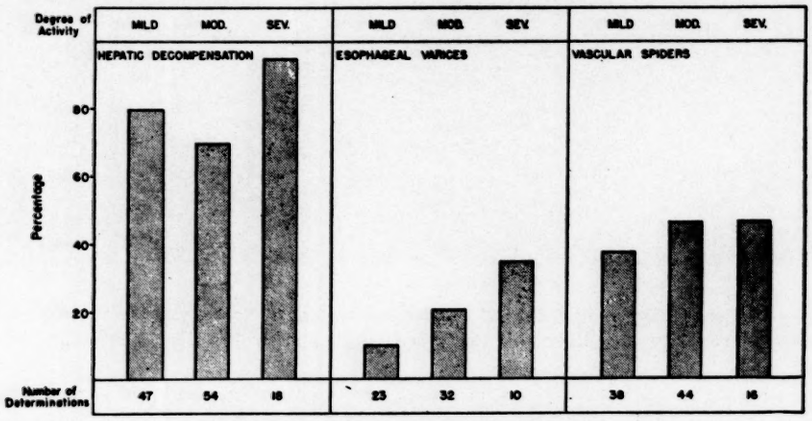


FIG. 4. Abnormal clinical findings and degree of activity.

3. *Spider Nevi.* Spider nevi were found in forty-one (42 per cent) patients and their absence specifically noted in fifty-seven others. They occurred with equal frequency in the nutritional, post-necrotic and portal groups. In Figure 4 it can be seen that "spiders" were found in fourteen (37 per cent) of thirty-eight patients, twenty (45 per cent) of forty-four patients and seven (44 per cent) of sixteen patients in the three ascending gradations of activity.

4. *Total Serum Proteins.* This was determined in seventy-three instances and found to be less than 6 gm. per cent in twenty-five (34 per cent). Figure 5 demonstrates very slight correlation between the level of total serum proteins and the degree of activity found in the biopsy specimens. Of twenty-eight patients with slight activity nine (32 per cent) had abnormally low values. In the group with moderate activity eleven (33 per cent) of thirty-three determinations were less than 6 gm. per cent. Five (42 per cent) of twelve instances showing marked activity had abnormal depression of the total serum proteins.

5. *Serum Albumin.* This was determined only forty-nine times and found to be less than 4 gm. per cent in forty-two (86 per cent) instances. In fourteen (82 per cent) of seventeen, twenty (87 per cent) of twenty-three and eight (89 per cent) of nine determinations in the ascending grades of activity the serum albumin was abnormally decreased. As shown in Figure 5, the level of the serum albumin was independent of the degree of activity noted in the biopsy specimen.

6. *Thymol Turbidity Test.* This was determined 114 times and found to be greater than 6 units in fifty-seven (50 per cent) instances. In Figure 5 it is seen that the thymol turbidity was abnormal in nineteen (40 per cent) of forty-seven determinations in patients with slight activity, in thirty-two (63 per cent) of fifty-one instances of moderate activity and in six (38 per cent) of sixteen instances of marked activity.

7. *Cephalin-Cholesterol Flocculation Test.* The results of this test are compared with the degree of activity observed in the biopsy specimen in Figure 5. One hundred twenty tests were made and in seventy-nine (66 per cent) the results were greater than 2+ in twenty-four hours. Over 50 per cent of the patients in all gradations of activity had abnormal cephalin-cholesterol flocculation tests. However, an ascending relationship between the degree of activity and the number of abnormal tests was noted. Twenty-seven (57 per cent) of forty-seven determinations in patients with mild activity were abnormal, as were thirty-eight (67 per cent) of fifty-seven instances of moderate activity. The most advanced degree of activity was observed in sixteen instances and in fourteen (88 per cent) the cephalin flocculation was abnormal.

8. *Total Serum Bilirubin.* This was deter-

mined in 115 instances and found to be over 1.2 mg. per cent in sixty-eight (59 per cent) of the cases. In general the total serum bilirubin followed a trend similar to that of the cephalin flocculation test. (Fig. 5.) Twenty-two (49 per cent) of forty-five patients with slight activity,

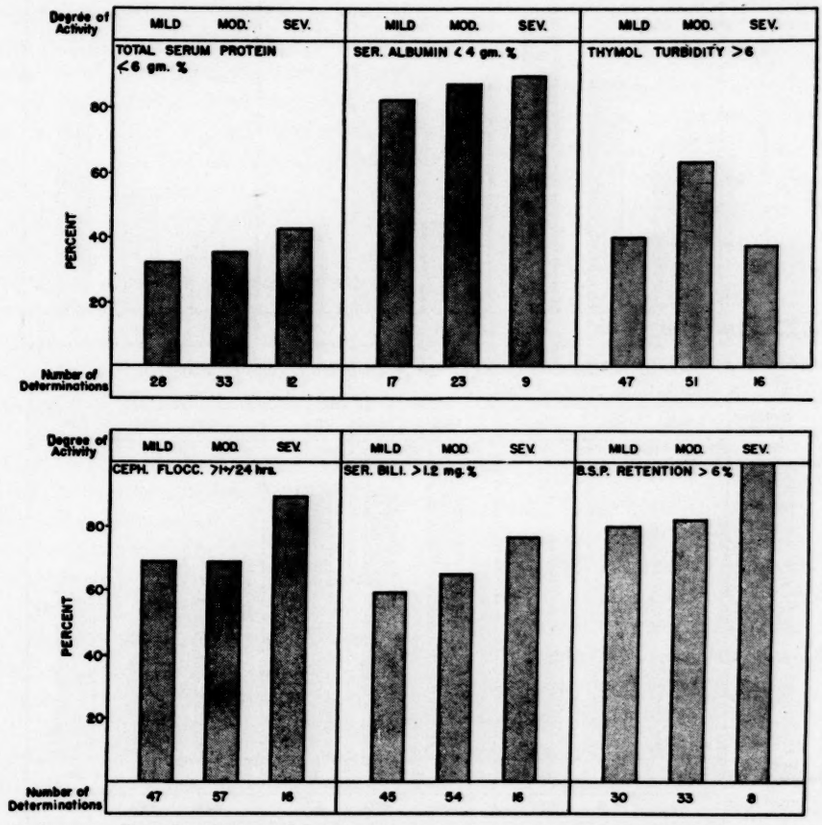


FIG. 5. Abnormal laboratory results and degree of activity.

thirty-four (63 per cent) of fifty-four patients with moderate activity and twelve (75 per cent) of sixteen patients with severe activity had abnormally elevated total serum bilirubin.

9. *Bromsulphalein Retention.* This was determined in seventy-one instances and found to be abnormal in fifty-eight (82 per cent). As shown in Figure 5, there is good correlation with the presence of liver disease *per se*, but dye retention is independent of the degree of activity. Abnormal BSP retention was found in twenty-three (77 per cent) of thirty determinations in patients with mild activity, in twenty-seven (82 per cent) of thirty-three with moderate activity and in all eight instances of severe activity.

Fibrosis

1. *Hepatic Decompensation.* In Figure 6 it is seen that evidence of decompensation was found in eight (42 per cent) of nineteen instances in which mild fibrosis was observed. The relationship rose in step-wise fashion to twenty-eight (70 per cent) of forty instances in patients with moderate fibrosis and fifty-five (92 per cent) of sixty instances in patients with severe fibrosis. The correlation of ascites, edema or clinical jaundice with the degree of fibrosis as seen in the biopsy specimen is striking.

2. *Esophageal Varices.* No obvious relationship between demonstrable varices and the degree of fibrosis was found as indicated in Figure 6. Three (27 per cent) of eleven patients with mild fibrosis, two (10 per cent) of twenty-one patients with moderate fibrosis and seven (21 per cent) of thirty-three patients with severe degrees of fibrosis were found to have demonstrable varices.

3. *Spider Nevi.* In a comparison of the

degree of fibrosis with the presence of vascular spiders a correlative trend could be seen, as demonstrated in Figure 6. Four (27 per cent) of fifteen patients with slight fibrosis had spiders as did eleven (thirty-four per cent) of thirty-two with moderate fibrosis and twenty-six (51 per cent) of fifty-one with severe fibrosis.

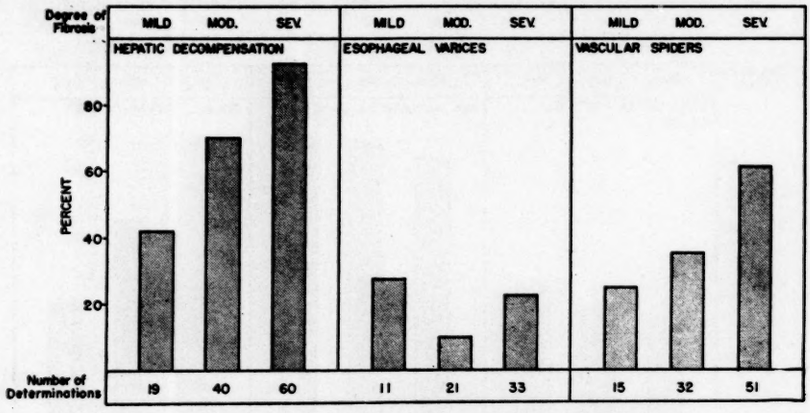


FIG. 6. Abnormal clinical findings and degree of fibrosis.

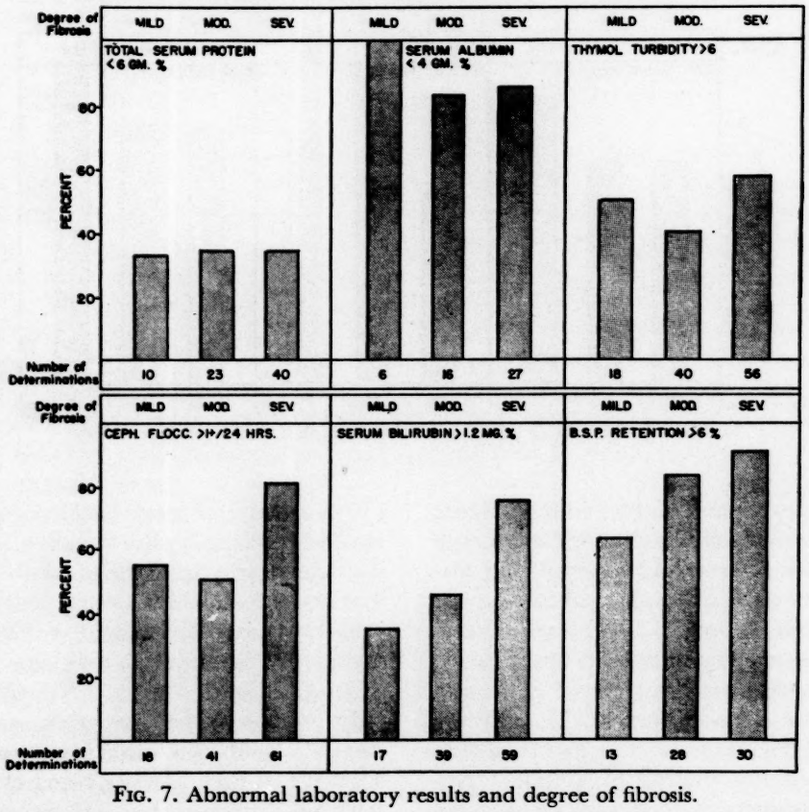


FIG. 7. Abnormal laboratory results and degree of fibrosis.

4. *Total Serum Proteins.* The serum protein levels seemed to be uninfluenced by the degree of fibrosis found in the biopsy specimens. (Fig. 7.) There were ten patients with slight fibrosis and three (33 per cent) had abnormally low total serum proteins. Of the twenty-three instances in which moderate fibrosis was found and total serum protein determined there was a depression below normal in eight (thirty-five per cent). In the group whose sections showed severe fibrosis fourteen (35 per cent) of forty determinations were abnormally low.

5. *Serum Albumin.* In relation to the extent

of fibrosis it was found that all six determinations made on patients with mild fibrosis were abnormally low, while thirteen (81 per cent) of sixteen with moderate fibrosis and twenty-three (85 per cent) of twenty-seven with severe fibrosis had abnormal depression of the serum albumin. (Fig. 7.)

6. *Thymol Turbidity Test.* Abnormal elevations of the thymol turbidity were poorly correlated with the presence of fibrosis. (Fig. 7.) Abnormal results were obtained in nine (50 per cent) of eighteen instances of minimal fibrosis, sixteen (40 per cent) of forty instances of moderate fibrosis and thirty-two (57 per cent) of fifty-six instances of severe fibrosis.

7. *Cephalin-cholesterol Flocculation Test.* The results of the attempts to correlate the cephalin flocculation with degree of fibrosis seen in biopsy specimens is recorded in Figure 7. In the groups with mild and moderate fibrosis, abnormal results were found in ten (56 per cent) of eighteen and twenty (49 per cent) of forty-one determinations, respectively. There were sixty-one instances of severe fibrosis, and in forty-nine (80 per cent) of these the cephalin-cholesterol flocculation tests were abnormal.

8. *Total Serum Bilirubin.* Figure 7 shows the pattern of relationship between the serum bilirubin level and the degree of fibrosis observed. Six (35 per cent) of seventeen determinations on patients with mild fibrosis had abnormal bilirubin levels as did seventeen (44 per cent) of thirty-nine with moderate fibrosis and forty-five (76 per cent) of fifty-nine with severe fibrosis.

9. *Bromsulphalein Retention.* The results of a comparison of degree of fibrosis and abnormal BSP retention are shown in Figure 7. In thirteen determinations in patients showing mild fibrosis eight (62 per cent) were abnormal. Twenty-three (82 per cent) of twenty-eight determinations in instances of moderate fibrosis and twenty-seven (90 per cent) of thirty determinations in the group with severe fibrosis were abnormal.

The method of analysis used in this study was based on the assumption that fibrosis and activity, each alone to a significant degree, affect the clinical picture or laboratory results in cirrhosis. This assumption was proved valid by an analysis of the available data considering each variable (fibrosis and activity) constant while studying the other. The results were in nowise different from the findings reported above.

COMMENTS

This review of 100 cases of cirrhosis of the liver has not revealed a satisfactory inter-relationship between clinical findings, laboratory results and the morphologic changes seen in liver biopsy specimens.

Hepatic decompensation was unrelated to the degree of activity noted histologically. On the other hand, a correlation was seen between decompensation and fibrosis.

The occurrence of esophageal varices in hepatic cirrhosis is accepted as a manifestation of portal hypertension due to "intrahepatic block.[27,28] This "block" is based, theoretically, on the presence of fibrosis. The findings of this study, however, suggest that the occurrence of demonstrable varices may be independent of the degree of fibrosis as found in needle biopsy specimens of the liver.

The slight increase in the number of patients with marked activity who had varices is not sufficiently significant to warrant any conclusions.

The occurrence of spider nevi was independent of the degree of activity of the disease. However, they did occur more frequently in patients with marked fibrosis.

The total protein content of the serum was below normal in only about one-third of the instances in which it was determined. There was no correlation between the total serum protein level and the degree of activity or extent of fibrosis observed histologically, as has been noted by others.[4,9,11] On the other hand, the serum albumin was abnormally depressed in 86 per cent of the determinations made in this series, and was independent of the degree of activity or fibrosis seen in biopsy specimens. This is contrary to the opinion of Volwiler et al.[17] that the serum albumin level accurately reflects the degree of degeneration and parenchymal cell regeneration in cirrhosis.[17]

The bromsulphalein retention in this series followed a pattern quite similar to that of the serum albumin.

The thymol turbidity test has been considered a good index of hepatic cell regeneration by Popper and others.[11,19] However, Mateer et al. believe that the test is of less value as a measure of hepatic impairment in cirrhosis than it is in acute hepatitis and that it is not valuable

as a diagnostic aid.[26] The results of this study would favor the latter opinion.

The close relationship between the cephalin-cholesterol flocculation test and the thymol turbidity test actually found or implied by others[4,11,19,29] was not demonstrated in this study. The thymol turbidity test appeared to be rather insensitive in portal cirrhosis generally.

The cephalin-cholesterol flocculation test tended to correlate with either activity or extent of fibrosis although it was abnormal in over one-half of the determinations in both categories regardless of degree. Popper has previously pointed this out.[4] Hanger and Patek[12] expressed the view that the prognosis in cirrhosis was grave when the cephalin-cholesterol flocculation test was "persistently positive." In the present group of patients thirty have died of hepatic decompensation, coma or bleeding esophageal varices. Twenty of these thirty patients had positive cephalin flocculation tests at the time of biopsy.

In general, the trend of the serum bilirubin followed that of the cephalin flocculation test. It, too, tended to be more frequently elevated with more advanced degrees of activity and fibrosis. A striking feature of this determination was that the highest levels (over 7 mg.) occurred in patients with severe degrees of fibrosis. However, the cephalin flocculation test appeared slightly more sensitive. Hanger and Patek[12] have cited their experiences in which the cephalin-cholesterol flocculation test was seldom negative in the presence of icterus. The findings of this study confirm their odservations.

SUMMARY AND CONCLUSIONS

1. An analysis of 100 patients with cirrhosis, in whom needle biopsy of the liver was performed, was undertaken in an attempt to find a clinical or laboratory pattern of aid to the clinician in assessing the degree of activity or the extent of fibrosis as revealed by needle biopsy.

2. The cases included in this series were classified as nutritional, post-necrotic and portal cirrhosis. One hundred twenty-three individual biopsies in the 100 patients were studied.

3. Each biopsy specimen was graded according to the degree of activity of the pathologic process and the extent of fibrosis.

4. "Decompensation" of the liver and spider nevi were most frequently associated with severe degrees of fibrosis but appeared to be unrelated to the degree of activity.

5. The presence of demonstrable esophageal varices was unrelated to the degree of activity or fibrosis although the number of cases in this category was small.

6. Serum albumin and bromsulphalein retention were found to be abnormal in the majority of determinations regardless of the degree of morphologic change.

7. The cephalin-cholesterol flocculation test and the total serum bilirubin were most frequently abnormal in cases with the greatest degrees of activity and fibrosis.

8. The thymol turbidity test and the total serum protein were found to be poor indices of either the degree of activity or fibrosis.

9. The clinical and laboratory criteria in common use do not reflect the degree of activity of the pathologic process or the extent of fibrosis present in individual cases of hepatic cirrhosis.

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Paraplegia and Secondary Amyloidosis*

Report of Six Cases

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With the advent of chemotherapy, antibiotics, improved surgical technics and extensive programs of coordinated rehabilitation the life expectancy of a patient with spinal cord injury, either paraplegic or quadriplegic, has been prolonged. Recent reports[1,2] have called attention to the occurrence of secondary amyloidosis in such patients. Thompson and Rice[1] noted the association of the triad of urinary tract infection, decubitus ulcers and chronic osteomyelitis with amyloidosis in four paraplegics. Bowman and Redfield[2] emphasized pyelonephritis as the common finding in four quadriplegic patients.

Six of the following seven cases offer additional confirmation of the association of amyloidosis with spinal cord injury. All were treated with various antibiotics and chemotherapeutic agents. Their survival time for the most part was longer than in those previously reported.[1,2]

CASE REPORTS

CASE I. Complete paraplegia developed in a twenty-five year old Negro following compression fracture of the first lumbar vertebra due to trauma. He was admitted to this hospital four months after the accident and observed until death sixty-two months later. Intravenous pyelogram showed a non-functioning right kidney nineteen months following the onset of paraplegia. Right ureterolithotomy did not improve function. Forty-five months after injury marked hematuria, fever and nausea occurred with a rise of his previously normal blood urea nitrogen (BUN) to 60 mg. per cent. Upon introducing a catheter into the left renal pelvis thick purulent material was aspirated and the BUN fell to 25 mg. per cent. Left pyelolithotomy and nephrostomy were performed. At fifty-one months of illness a scrotal abscess developed. It was incised and drained and the patient finally required left epididymectomy and right orchiectomy. He became uremic and oliguric and expired sixty-six months after the onset of paraplegia. Urinary cultures during life yielded a variety of organisms including Bacillus proteus, Escherichia coli and Aerobacter aerogenes. Ascites or edema never developed. Decubitus ulcers were a constant problem, some healing spontaneously, others requiring plastic repair. The patient was free of decubitus ulcers between the forty-ninth and fifty-fifth months of his course.

Autopsy findings were as follows: compression fracture, first lumbar vertebra; myelomalacia, mid-thoracic region; hypoplasia, right kidney (50 gm.); bilateral pyelonephritis; bronchopneumonia; prostatitis, acute, suppurative; cystitis, acute, suppurative; abscesses of scrotum, multiple; amyloidosis (Figs. 1 and 2), liver, spleen, adrenals, kidneys and thyroid.

CASE II. A twenty-five year old white man sustained a gunshot wound with fracture of the eighth dorsal vertebra and the left humerus with immediate paralysis from the waist down. A peculiar feature was the persistence of a flaccid rather than a spastic paralysis with a level as high as the seventh thoracic segment. Decubitus ulcers developed within three weeks after injury and were a constant and difficult problem. The patient was admitted to this hospital twenty-four months following injury and was observed intermittently until death. Repeated attempts at plastic repair of the decubitus ulcers were of no avail. Osteomyelitis was evident in the humerus and in both ischii. Urinalyses varied from 0–4 plus albuminuria tending towards 4 plus late in the course of his illness. Specific gravity was fixed forty-four months after trauma, but BUN and urea clearance were still normal at that time. Shortly thereafter the BUN began to rise, reaching 103 mg. per cent shortly before death. Urine cultures were positive for B. pro-

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teus, A. aerogenes, Esch. coli and streptococci. There were variations in the serum proteins with a fall in albumin and rise in globulins in the later months. There was no edema or ascites. Intravenous pyelogram fifty-three months after injury revealed right nephrolithiasis and left hydroureter and hydronephrosis. Repeat intravenous pyelogram ten months later showed a poorly functioning left kidney with marked right hydronephrosis. The patient died in uremia, eighty-eight months following the onset of paraplegia..

Autopsy findings were as follows: degeneration, gliosis and atrophy of 7th and 8th thoracic segments of spinal cord with adhesions of dura and leptomeninges in the same area; ascending degeneration of sensory tracts; myelomalacia below 8th thoracic segment; decubitus ulcers, multiple, severe; pyelonephritis, bilateral; pyonephrosis, left; cystitis; fibrinous pericarditis (uremic); bronchopneumonia; amyloidosis (Figs. 1 and 2), liver, spleen, adrenals and kidneys.

Case III. A twenty-eight year old white man sustained a gunshot wound of the spine with fracture of the ninth thoracic vertebra followed by immediate paralysis of both lower limbs. Shortly afterwards exploratory laminectomy was performed. The line of sensory impairment descended from the nipple line to the lower ribs postoperatively. At this hospital, six months later, the patient exhibited a spastic paraplegia, bowel and sexual impairment, and a neurogenic bladder. He was able to spend long intervals at home. Small decubitus ulcers responded to surgical and supportive measures. The patient had a suprapubic cystotomy performed one week after injury and thereafter refused reparative surgery. Left renal and vesical calculi were noted forty-one months after the accident. BUN determinations were normal throughout his course. Urine examination usually showed a trace of albumin with leukocytes and erythrocytes ranging from none to many. Urine cultures were persistently positive for A. aerogenes, B. proteus and Esch. coli. One week before death diarrhea and tachycardia developed and the patient went into shock. He died sixty-one months after the onset of paraplegia.

Autopsy findings were as follows: degeneration of spinal cord in the region of the eighth thoracic segment; epidural abscess at laminectomy site; acute bacterial endocarditis, mitral valve (due to gram-positive cocci); endocardiosis, aortic and mitral valves; pyelonephritis, bilateral; infarction of spleen, multiple, septic; jejunitis, hemorrhagic; amyloidosis (Figs. 1 and 2), liver, spleen, adrenals, kidneys and pancreatic vessels.

Case IV. A twenty-one year old white man was hit in the back by shell fragments and quadriplegia developed. One week later he recovered the use of his upper extremities. Laminectomy was performed one month later with removal of metallic fragments at the level of the fourth to sixth thoracic vertebrae. There was no objective change following laminectomy. At this hospital, six months later, he was found to have a spastic paraplegia. Large decubitus ulcers were present on both hips and were resistant to therapy and attempts at plastic repair. Severe anemia persisted despite frequent transfusions. Intravenous pyelogram showed dilatation of ureters and calyces. BUN was always normal. Urine examinations revealed 2 plus albuminuria with few to many white blood cells. Urine cultures were positive for A. aerogenes, Esch. coli and hemolytic and non-hemolytic streptococci. The serum albumin was relatively normal but elevated globulin levels developed. Edema and ascites never developed. The patient suddenly complained of severe substernal distress fifty-nine months following the advent of paraplegia. Cardiac dullness was increased in area, with diffuse heart action and muffled heart sounds. A diagnosis of pericardial effusion was entertained but the patient died suddenly before diagnostic studies were completed.

Autopsy findings were as follows: degeneration spinal cord, fifth to seventh thoracic segments; pericardial effusion, hemorrhagic (1,100 cc.); decubitus ulcers, multiple, severe; pyelonephritis, bilateral; cystitis, acute and chronic; amyloidosis (Figs. 1 and 2), liver, spleen, adrenals and kidneys.

Case V. Signs and symptoms of multiple sclerosis developed in a twenty-four year old white man. At age twenty-eight he was admitted to this hospital with severe spastic contractures of both legs, complete spastic paraplegia below the ninth thoracic vertebra, paresis of the left arm, diplopia, intention tremors, scanning speech, urinary and fecal incontinence and huge multiple decubitus ulcers. Laminectomy with bilateral section of the posterior columns in the region of the ninth and tenth thoracic cord segments afforded no relief of his spasms and contractures. Injection of 15 cc. absolute alcohol in the first lumbar subarach-

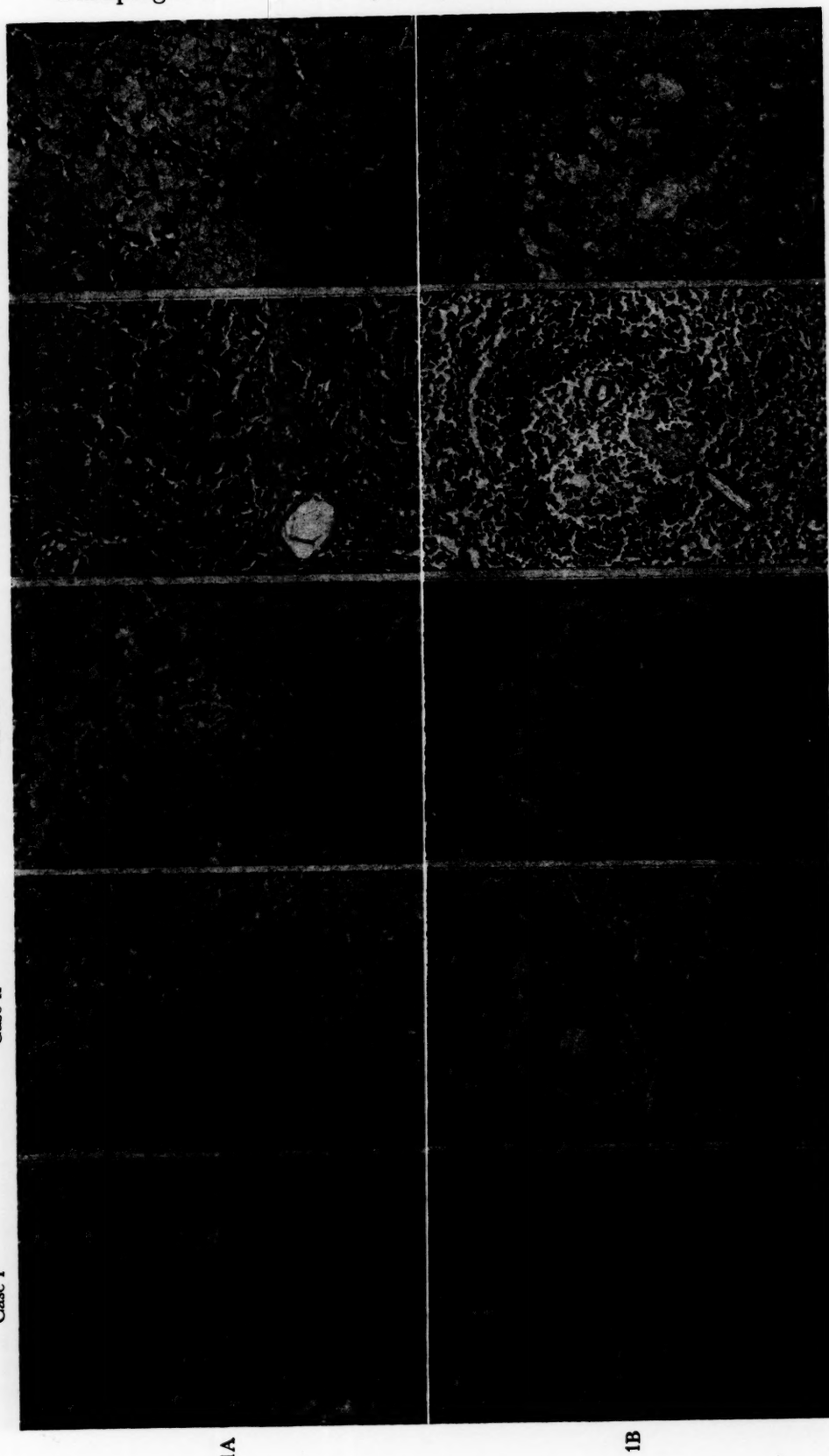


FIG. 1. A, liver showing typical secondary amyloidosis; B, spleen showing secondary amyloidosis (Case IV shows minimal amount of amyloid; arrow indicates trabecula. not amyloid); hematoxylin and eosin × 100.

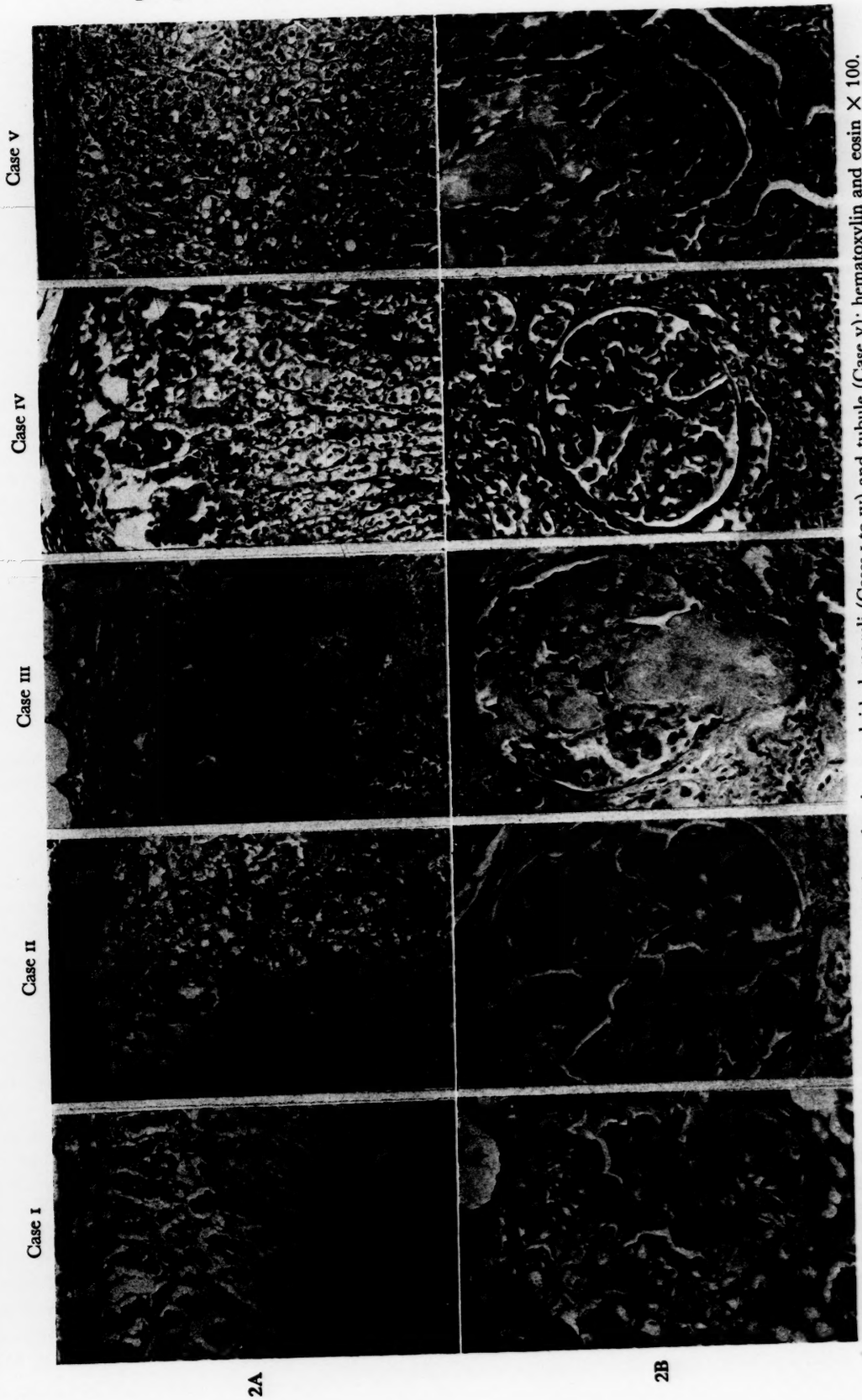
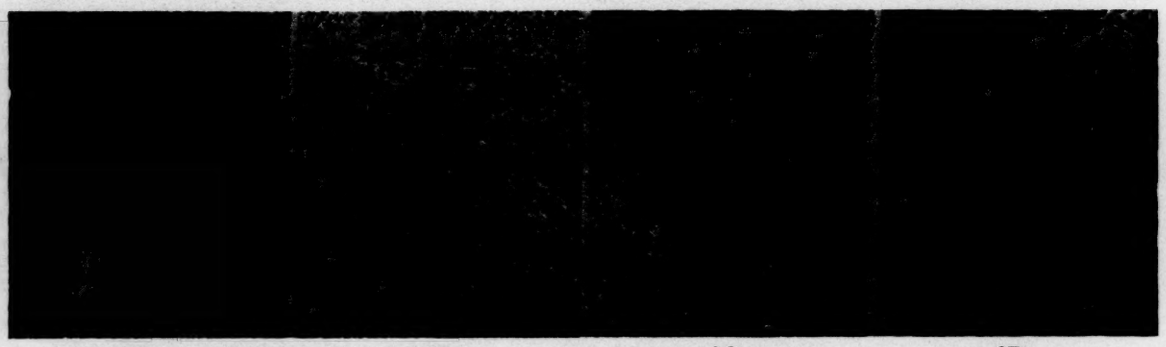


FIG. 2. A, adrenal, secondary amyloidosis; B, kidney showing amyloid glomeruli (Cases I to IV) and tubule (Case V); hematoxylin and eosin × 100.



3A 3B 3C 3D

FIG. 3. Case VI. A, liver; B, spleen; C, adrenal; D, kidney. Amyloid in spleen, adrenal and kidney. Liver shows hepatitis with necrosis, not amyloid; hematoxylin and eosin × 100.

noid space was performed and afforded complete relief of the spasms of the lower extremities. The contractures and decubitus ulcers did not respond to treatment. Urine examinations showed 0–2 plus albumin, with occasional white blood cells and erythrocytes. Urine cultures were intermittently positive for Pseudomonas aeruginosa, B. proteus, streptococci and staphylococci. BUN was never elevated. Shortly after admission, blood proteins showed a rise in globulin. The patient had persistent fever and died twenty months following the onset of paraplegia.

Autopsy findings were as follows: multiple sclerosis, manifested by scattered areas of focal demyelinization and astrocytosis, brain and spinal cord; bronchiectasis, left lower lobe; pyelonephritis, bilateral; cystitis; bronchopneumonia; decubitus ulcers, massive; amyloidosis (Figs. 1 and 2), liver, spleen, adrenals, kidneys and lymph nodes.

CASE VI. At age twenty-three this white man sustained multiple rib fractures and injuries to the ninth and tenth thoracic vertebrae in a train accident. When admitted to this hospital six months after the injury, he had spastic paraplegia, neurogenic bladder, fecal incontinence and a sensory level at D-11. Laminectomy was performed four months following hospital admission because of partial spinal block but no improvement resulted. Repeated attempts at plastic repair of the severe decubitus ulcers were unsuccessful and osteomyelitis of the upper end of the left femur and pelvis finally necessitated disarticulation of the left lower extremity at the hip. Despite this procedure decubitus ulcers remained a serious problem. Sixty-nine months after injury homologous serum hepatitis associated with the syndrome of lower nephron nephrosis supervened. The patient recovered from this episode. One hundred one months following injury the patient sustained a compound, comminuted fracture of the right femur in an automobile accident. Soft tissue abscesses and osteomyelitis developed and both responded to incision and drainage. The patient had persistent anemia. Except for an elevation of BUN during the earlier episode of lower nephron nephrosis, BUN levels were within normal limits until the last few months of life. Prior to the last thirty months of life urine examinations had shown only faint traces of albumin and a few white blood cells. Urine cultures were persistently positive for a variety of organisms including Esch. coli, A. aerogenes, B. proteus, alpha streptococci and hemolytic Staphylococcus aureus. Four plus albuminuria developed, with many white blood cells and red blood cells in the urine. One hundred ten months after the initial injury a large left ischial abscess developed. It was opened and drained a large amount of foul-smelling pus. The patient became febrile, uremia supervened and death occurred 111 months after the onset of paraplegia.

Autopsy findings were as follows: degeneration of spinal cord, seventh and eighth thoracic segments; adhesive arachnoiditis; bronchitis and bronchiolitis, suppurative; decubitus ulcers, multiple; osteomyelitis of sacrum, secondary to decubitus ulcers; cystitis; hepatitis with necrosis and focal atrophy; amyloidosis (Fig. 3), spleen, adrenals and kidneys.

CASE VII. A fifty-eight year old white man was admitted to this hospital because of hematemesis and melena. He had a history of alcoholism, essential hypertension and duodenal ulcer since 1922. A subtotal gastrectomy was performed. Two days later signs of an upper motor

neuron lesion developed with weakness of both lower extremities, hyper-reflexia and low back pain. Areflexia, loss of motor power of the lower extremities and priapism soon supervened. The clinical diagnosis was intramedullary bleeding either apoplectic or thrombotic in origin. Improvement began one week later with almost complete recovery in three weeks, the only residua being numbness and inability to extend the thighs. The patient began walking one month later and was discharged four months after admission. Two years later he was readmitted with a history of six months of progressive stiffness of the legs, lumbar pain and occasional urinary incontinence. Paraparesis with sphincter and sensory disturbances, the latter below T-8 bilaterally, were noted. Urine showed fixed specific gravity at 1.010, 0–2 plus albuminuria and occasional white blood cells and erythrocytes. Laminectomy at T-8 was performed two months after this admission. Adhesive arachnoiditis with poor pulsations of the cord below the adhesions were noted. The adhesions were split following which better pulsation was noted in the lower cord. Physical rehabilitation was attempted postoperatively but proved unsuccessful. The paraparesis progressed to complete paraplegia eighteen months before death. There were never any decubitus ulcers throughout this patient's course. Pyelograms showed dilatation of the right kidney pelvis and a reduplication of the left ureter. Urine cultures were frequently positive for a variety of organisms including A. aerogenes, B. proteus and alpha and gamma streptococci. BUN was normal until the last twelve months of life when it ranged between 35–40 mg. per cent. Serum proteins were normal. The patient died suddenly eighteen months after the onset of complete paraplegia.

Autopsy findings were as follows: syringomyelia from the level of T-5 through the lumbar segments; adhesive arachnoiditis, T5–T8; focal myocardial necrosis; marginal ulcer, gastrojejunostomy site; Laennec's cirrhosis, early; cholangiolitis; pneumonia, granulomatous (aspiration ?); pyelonephritis, bilateral; nephrolithiasis; cystitis, chronic; prostatitis, chronic, non-specific.

COMMENTS

Bowman and Redfield[2] reported four cases of amyloidosis in quadriplegics and concluded that pyelonephritis was the single most important factor in the genesis of amyloidosis, with decubitus ulcers "possibly contributing an added factor." Thompson and Rice[1] noted the triad of urinary tract infection, decubitus ulcers and osteomyelitis. Several of the seven cases aforementioned have had much longer courses than those previously described,[1,2] lasting up to 111 months. Secondary amyloidosis was found at autopsy in six of the seven cases. Severe pyelonephritis was present in the one case without amyloidosis (Case VII) and one of the patients with paraplegia and amyloidosis had no evidence of pyelonephritis (Case VI). Urinary tract infection was present in all seven cases and osteomyelitis in two. The distinguishing feature in the one case without amyloidosis (Case VII) was the absence of decubitus ulcers or other extensive suppurative foci during the course of the illness.

A statement[2] of the association of pyelonephritis with secondary amyloidosis led to a survey of the autopsy material at this hospital. In 2,550 autopsies 161 cases presented gross and microscopic evidence of pyelonephritis. The only cases among the 161 in which the combined diagnoses of amyloidosis and pyelonephritis were made were the first five cases described previously. In addition six other cases of extensive secondary amyloidosis unassociated with either pyelonephritis or paraplegia were reviewed. One was due to long-standing rheumatoid arthritis, one to cavitary pulmonary tuberculosis, one to a combination of rheumatoid arthritis and tuberculosis; the fourth was associated with generalized arteriolocapillary thrombonecrosis, hemoglobinuric nephrosis, luetic aortitis and schistosomiasis; the fifth case in which the amyloid was confined almost exclusively to the liver was associated with an epidermoid carcinoma of the left lower lobe bronchus with extensive necrosis and suppuration of the tumor, and luetic aortitis; the sixth case had chronic urethral strictures with multiple diverticuli, periurethral abscesses with multiple draining sinuses, luetic aortitis, general paresis with granular ependymitis and an old ununited fracture of the left femoral neck with osteomyelitis.

The association of amyloidosis with chronic suppurative disease is well known. To attribute the development of amyloidosis in spinal cord injury to pyelonephritis in particular seems unjustified on the basis of our experience. Weiss and Parker[3] noted no such association in their classic review of pyelonephritis. Many of their cases were of long duration.

It would seem that the total mass of suppurative disease rather than any single focus was associated with the development of amyloidosis in the present series. The relatively long duration of life of the patients in this group may be attributed to the energetic attack by medical and surgical means on recurring areas of infection. The seventh case reported in this series suggests that success in avoiding the development of amyloidosis depends on limitation of suppurative disease to as small an area as possible. Although little can be done in the immediate post-traumatic period as regards the necessity for suprapubic cystotomy or indwelling catheter drainage with inevitable urinary tract infection, attention must be directed in the subsequent period to measures which eliminate the necessity for catheter drainage. The question arises whether decubitus ulcers can be prevented even by superlative nursing care in the immediate post-trauma period. It is evident from this series that this is the source of a large area of suppuration.

SUMMARY

Seven patients with paraplegia, the duration of which ranged from 18 to 111 months, are presented in this report. Six of the seven presented the typical findings of secondary amyloidosis at autopsy. All six had decubitus ulcers of varying severity during life and five had pyelonephritis, cystitis and prostatitis. The sixth patient had no pyelonephritis but his decubitus ulcers were multiple, large and severe. Two patients had osteomyelitis, one a scrotal abscess and one an epidural abscess and terminal acute bacterial endocarditis. The seventh patient had no amyloidosis at autopsy, did have pyelonephritis, cystitis and prostatitis but had no decubitus ulcers throughout his course. It is suggested that the total mass of suppurative disease rather than any single focus was associated with the development of amyloidosis in the six cases and that success in avoiding the development of amyloidosis in patients with paraplegia depends on limitation of suppurative disease to as small an area as possible.

Acknowledgments: We wish to thank Dr. Benjamin S. Gordon, Chief, Laboratory Service, Bronx Veterans Administration Hospital for permission to use these cases. Our thanks are due also to Mr. Sidney Shapiro, Medical Illustration Division, Bronx Veterans Administration Hospital for the photomicrographs and plate mountings.

Addendum: Since submitting this article we have observed three additional cases of amyloidosis, two in paraplegics of seventy-five and ninety-six months' duration and one in a quadriplegic of nineteen months' duration. All three had severe and extensive decubitus ulcers. The latter two died and at autopsy pyelonephritis and amyloidosis of spleen, kidneys and adrenals were revealed. The first patient is still alive, has evidence of pyelonephritis and on liver biopsy demonstrated marked amyloid infiltration.

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Review

Varicella Encephalitis*

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VARICELLA has usually been considered a mild, self-limited disease, associated with few complications. In recent years, however, considerable attention has been directed to central nervous system and visceral involvement in chickenpox. Occasional reports of varicella encephalitis have appeared from time to time since Hunter's[1] description of a case in 1875 but the first comprehensive paper on the subject was published by Underwood[2] in 1935. In that report the author collected 119 cases from the literature and added one of his own. A number of detailed clinical records have since appeared.[3–19]

Etiology. The etiology of varicella encephalitis is unknown. The most commonly held views are: (1) that the disease is due to invasion by the virus of varicella; (2) that the condition is due to an allergic response of the central nervous system to the virus of varicella (the hypersensitivity theory); (3) that the varicella virus activates another virus which is dormant in the patient (the activation theory); and (4) that the occurrence of encephalitis is a coincidence and unrelated to chickenpox.

Pathology. Review of the literature on encephalitis in otherwise uncomplicated cases of varicella yields only six cases confirmed by histologic findings.[10,12,15,20–23] Several other cases of varicella with neurologic manifestations that came to necropsy were found to have either purulent meningitis or were instances of varicella in patients with a chronic disease of the central nervous system; in some varicella was preceded by some other infectious disease or was complicated by some septic condition.

The histologic findings in the six clear-cut cases are summarized in Table 1. In all cases damage to the myelin was shown which varied from perivascular loss of myelin to severe softening of the white matter and some softening of the gray matter, as in the case of Swan.[15] Axonal damage was reported in two instances (Waring et al.,[12] Swan[15]). Microglial proliferation was noted in three cases (van Bogaert,[20,21] Waring et al.,[12] Swan[15]). Inflammatory perivascular infiltration with round cells or fat-containing phagocytes was present in every case. Degenerative changes in the neurons were observed in three instances.[15,20–22] In one instance there was evidence of concomitant diffuse vascular disease. This was the case of an adult[12] who showed the presence of chronic arteriolar disease of the brain and kidneys in addition to perivascular infiltration and damage to the myelin and axis cylinders.

We had the opportunity of examining the brain in a case of varicella that presented a clinical picture of encephalitis (convulsions, coma, absence of superficial reflexes, temperature up to 108°F.; the spinal fluid contained forty-nine lymphocytes). There was no loss of myelin in any part of the brain (Fig. 1) or spinal cord, although there was some marginal edema in the white and gray matter bordering on the blood vessels. There was an increased number of mononuclear cells in the walls of a few veins in one claustrum but the cuffs were from one to three cells deep (Fig. 2) and in some sections did not surround the vein completely. (Fig. 1.) The nerve cells were well preserved and no glial nodules were found. These changes were too slight to permit a histologic diagnosis of encephalitis.

ORIGINAL OBSERVATIONS

Case Material. The material in the present study consisted of fifty-nine cases of varicella encephalitis. Thirty-two of these cases were observed at the Willard Parker Hospital from March, 1938, to April, 1952, and twenty-seven cases were seen by the staff of the Division of Acute Infections of the Central Nervous System

* From the Willard Parker Hospital and the Bureau of Laboratories, New York City Department of Health, New York, N. Y.

of the New York City Health Department from February, 1931, to May, 1951. The material included one necropsy study already referred to and follow-up observations on thirty-three patients.

an incidence of 0.26 per cent. This figure is probably too high since the patients admitted to the hospital are, as a rule, more severe. It is generally recognized that varicella encephalitis is less common than measles encephalitis, which

TABLE I

HISTOLOGIC CHANGES IN SIX CASES OF VARICELLA ENCEPHALITIS

Author and Year	Age	Sex	Days of Neurologic Manifestations	Changes in White Matter	Changes in Gray Matter	Damage to Neurons	Glia
van Bogaert (1930, 1932)	12 yr.	F	17	Demyelination; inflammatory foci at border of white and gray matter	Perivascular cuffing	"Dusty" Nissl substance; "glassy" Purkinje cells, neuronophagia in globus pallidus	Some satellitosis; glial nodules in pallidum, in parietal and frontal regions
Zimmerman and Yannet (1931)	13 mo.	F	2	Demyelination—severe, perivascular, associated with formation of fat granular cells	In places loss of some ganglion cells	Swollen cells, with vacuoles; loss of Nissl bodies, but cell processes stain deeply, are visualized over great distance; some loss of neurofibrils; displaced nuclei	No proliferation
Dagnelie and Dubois (1932)	8 mo.	F	1	Perivascular demyelination, mainly in right parietal lobe; fat-containing phagocytes around blood vessels	Some granular phagocytes in basal ganglia	Normal	No proliferation
Bergman and Magnusson (1939)	12½ yr.	M	4	Small foci of degeneration infiltrated with round cells	Perivascular round cell infiltration in basal ganglia and medulla	Not mentioned	Not mentioned
Waring, Neubuerger and Geever (1942)	40 yr.	M	4	Fresh perivascular demyelination in places; petechiae and ring hemorrhages around central necrosis; slight cuffing of long veins with iron-filled macrophages; axons slightly damaged	Not mentioned	Normal	Swollen satellites and microglia; radial proliferation of microglia in areas of necrosis of white matter
Swan (1946)	6½ yr.	M	2 wk. plus	Perivascular softening and demyelination; degeneration of axis cylinders; perivascular cuffing	Gross softening in basal ganglia; perivascular cuffing in basal ganglia and cortex	Loss of nerve cells; swelling, chromatolysis, eccentric nuclei, a few degenerated cells in spinal cord	Microglia and gitter cells abundant in areas of tissue damage; also some "gemastete" astrocytes

Age. Varicella is essentially a disease of childhood and the complication of encephalitis also occurs most frequently in this period. In our series of cases 95 per cent of the patients were not more than eleven years of age. Only three patients were over twenty-one. The age of our youngest patient was eight months and the oldest patient was seventy-one years. Most of the patients ranged in the age group between five and seven years.

Sex. Of our patients 70 per cent were male.

Incidence. There is no reliable statistical information regarding the incidence of varicella encephalitis. Of 6,774 cases of varicella admitted to the Willard Parker Hospital from 1941 to 1950 eighteen were complicated by encephalitis, has an incidence of slightly less than one case per thousand.

Time of Onset. The relation of the onset of encephalitis to the first appearance of the rash is shown in Figure 3. It will be noted that 65 per cent of our cases occurred between the third and eighth posteruptive days. One case was coincident with the rash. Occurrence on the fourth posteruptive day was most frequent. The longest interval between appearance of the rash and the onset of the encephalitis was twenty-one days.

Mode of Onset. The disease was often ushered in dramatically with headache, vomiting, fever and a change in the sensorium, and in many instances with convulsions and paralysis as well.

FIG. 1. Section from the region of the claustrum; myelin undamaged around a vein showing incomplete mononuclear infiltration of its wall; myelin stain.

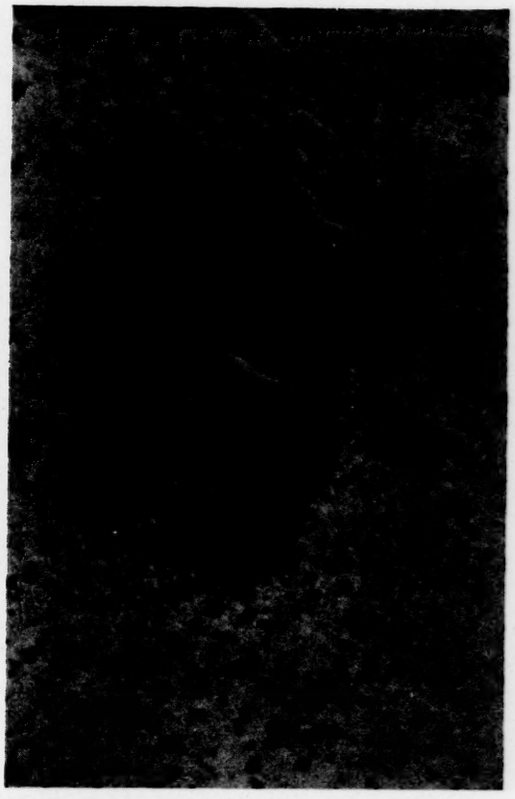

FIG. 2. Section from the region of the claustrum; infiltration of the wall of a vein with mononuclear cells. Slight edema of the adjacent brain tissue; hematoxylin and eosin.

This acute mode of onset occurred in thirty of our cases. The neurologic examination most commonly revealed stiffness of the neck and positive Kernig, Brudzinski and Babinski signs. The clinical picture reflected an acute meningoencephalitic insult. In twenty patients the mode of onset was more gradual and the predominating symptoms were irritability, drowsiness and ataxia. In nine cases the precise manner of onset was not noted.

Temperature. Elevation of temperature was present in thirty-nine patients. The fever was usually moderate and the temperature curve pursued no characteristic course. In some cases it returned to normal within twenty-four hours. In most cases, however, it remained elevated for a few days. There was no fever in twenty cases. Temperatures above 104°F. were noted in only seven instances.

Clinical Course. Since the pathologic process is diffuse and varies greatly as regards both the area involved and the intensity of the insult, the clinical course of the disease was likewise variable and almost every sign and symptom indicative of involvement of the central nervous system was encountered. (Table II.) We wish to emphasize the frequent occurrence of a change in sensorium in the early phase of the disease. However, a clear mental state was present in twelve cases and stupor was noted in only six instances. Personality changes in the acute stage were observed in a few cases and consisted usually of restlessness and irritability. Except for one instance of delirium, psychotic reactions were not noted. Convulsions were tonic or clonic, generalized or Jacksonian. Twitching of muscles, tremors of the hands or choreiform movements were observed in a few patients. Urinary retention occurred in seven cases and urinary incontinence in four cases. Abdominal pain was a major symptom in two instances. As the early acute phase of the illness subsided the extent of neurologic involvement, when present, became more apparent.

As noted previously the neurologic examina-

tion in the acute phase of the illness most commonly revealed signs indicative of meningeal irritation. The reflexes were variable. The deep tendon reflexes were more often exaggerated than diminished. A positive Babinski sign was found in ten patients and ankle clonus in three.

Spinal Fluid Findings. A spinal tap was done at least once in all cases but two. The results of the spinal fluid examinations are shown in Table III. The fluid was clear in the great majority of instances and was frequently under moderately increased pressure. A moderate increase in the number of white cells was the commonest abnormal finding. In only ten cases was the pleocytosis more than 100 cells per cubic millimeter. A cell count of 500 or more occurred in six cases. The highest cell count in this series was 2,795. Sixteen cases had a normal spinal fluid cell count. The differential cell count usually showed a predominance of lymphocytes but in three cases the polymorphonuclear cells predominated. There was a slight to moderate increase in the protein content in

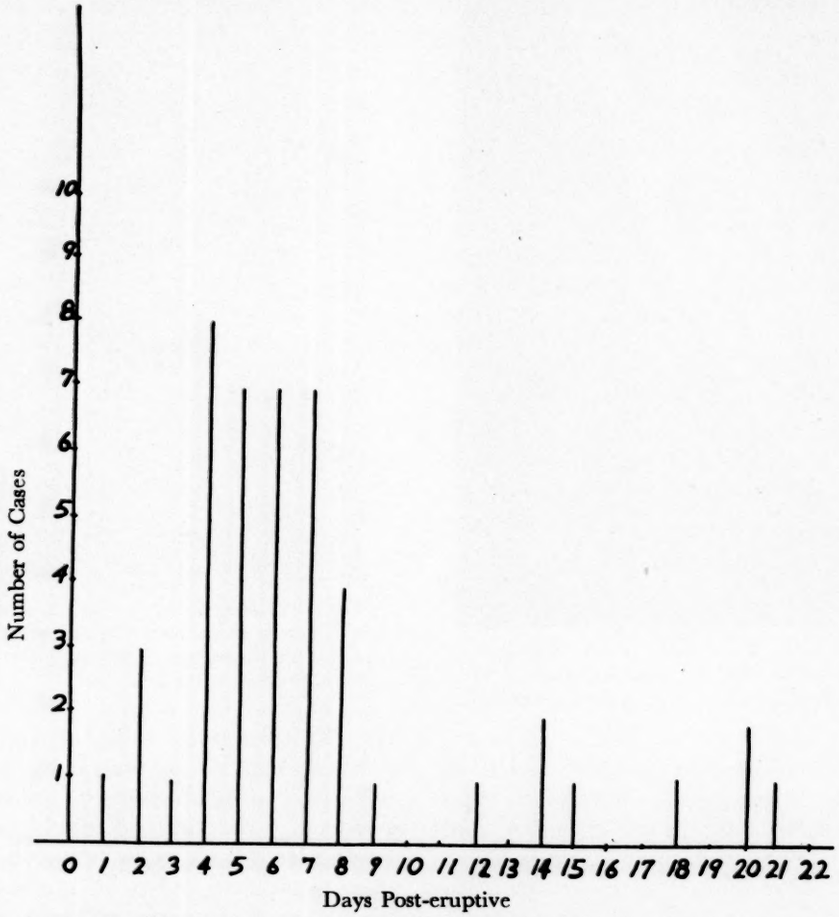

FIG. 3. Chart showing onset of varicella encephalitis in relation to the first appearance of the rash.

Pupillary changes were noted in ten instances. Blindness was encountered in one case. Strabismus was noted in six and nystagmus in seven patients. The seventh cranial nerve was involved in seven cases and impairment of speech was noted in seven others. Five patients had spastic paraplegia and four had a flaccid paraplegia. Hemiplegia was observed in two cases. Of particular interest was the occurrence of ataxia in eighteen patients. The prominence of cerebellar signs in varicella encephalitis has been noted by others.[2,19] There were two instances of hyperesthesia and two of hypesthesia. Mental retardation and personality changes were infrequent. In some cases the final clinical outcome was in doubt until considerable time had passed.

thirty cases. The sugar level was normal or elevated in all but one of the cases. Smears and cultures for micro-organisms were negative in all cases.

Differential Diagnosis. Meningitis, poliomyelitis, subarachnoid hemorrhage, other encephalitides, brain tumor and meningism may at times be confused with varicella encephalitis. Tuberculous meningitis, with drowsiness or stupor, may closely simulate varicella encephalitis. In the differential diagnosis careful attention must be paid to the history and results of the examination of the spinal fluid. The outstanding differential point is the occurrence of clinical manifestations of encephalitis in chronologic association with an attack of varicella.

Outcome. In our series of fifty-nine patients with varicella encephalitis three died, a mortality rate of 5 per cent. In each of these persons death occurred within the first week of illness. Two of the patients who died also had pneumonia and the third had signs of medullary involvement. Forty-seven patients (80 per cent) were discharged from the hospital without any neurologic or other detectable abnormalities. Nine patients (15 per cent) showed at the time of discharge residual central nervous system stigmas, which included paralysis, ataxia, blindness, mental retardation, disturbance of speech and personality changes. The average number of days of hospitalization for the uncomplicated group of patients was ten and for the group with residua twenty-four.

Our follow-up study consisted of observations on thirty-three patients. The results of this study are presented in Table IV. The shortest follow-up period was six months and the longest was thirteen years. For twenty-two of the patients the follow-up period was one year or longer. Twenty-three of the thirty-three patients escaped without any residual symptoms. In the remaining ten patients there were neurologic sequelae.

In the follow-up study it was of particular interest to investigate the development of changes in the patients subsequent to discharge from the hospital. The results of that investigation are shown in Table V. It will be seen that among twenty-four patients who were discharged without residua no abnormality was discovered subsequently in twenty-one instances. In the remaining three cases neurologic disturbances appeared six months after discharge in two instances and three years following discharge in the third patient. It will also be noted that among nine patients discharged with residual symptoms the sequelae later disappeared completely in two instances and partially in two

TABLE II
SIGNS AND SYMPTOMS IN FIFTY-NINE CASES OF VARICELLA ENCEPHALITIS

	No. of Cases
Meningeal Irritation	
Stiffness of neck	29
Kernig sign	16
Brudzinski sign	22
Headache	33
Vomiting	34
Fever	39
Sensorium	
Drowsiness	27
Stupor	6
Semi-stupor	5
Apathy	15
Irritability	7
Delirium	1
Euphoria	1
Cranial Nerves	
Anisocoria	1
Fixed dilatation of pupils	3
Sluggish reaction of pupils to light	6
Strabismus	6
Ptosis of lids	1
Paralysis of the facial nerve	7
Blindness	1
Motor Power and Coordination	
Spastic paraplegia	5
Flaccid paraplegia	4
Hemiplegia	2
Convulsions	13
Tremor of hands	2
Intention tremor	1
Choreiform movements	2
Abdominal twitching	1
Ataxia	18
Romberg sign	4
Nystagmus	7
Sensation	
Abdominal pain	2
Hyperesthesia	2
Hypesthesia with sensory level	2
Reflexes	
Deep reflexes exaggerated	14
Deep reflexes diminished	10
Deep reflexes absent	4
Babinski sign	10
Ankle clonus	3
Muscle tonus	
Hypertonus	12
Hypotonus	11
Bladder and bowel	
Urinary retention	7
Urinary incontinence	4
Fecal retention	4
Miscellaneous	
Aphasia	1
Slurred speech	6
Photophobia	2
Herpes zoster	1

TABLE III

SPINAL FLUID FINDINGS IN VARICELLA ENCEPHALITIS

Case No.	Cell Count	Lymphocytes (%)	Protein		Sugar	
			Qualitative*	Quantitative, (mg./100 cc.)	Qualitative†	Quantitative, (mg./100 cc.)
1	4	100	±			85
2	1,410	95	+		+++	
3	625	93	+		+++	
4	Bloody		+		+++	
5	75	95	+		+++	
6	Increase	90	+		+++	
7			+			110
8	895	70	+		+++	
9	40	100	+		+++	
10	15	100	+		+++	
11	45	100	+		+++	
12	Increase	Increase	+		+++	
13	45	100	+		+++	
14	Increase	98	+		+++	
15	65	10	±		+++	
16	35	95	+		+++	
17	Spinal tap not done					
18	50	98	+			126
19	1,910	90	+		+++	
20	2,795	35	++		+++	
21	8	100	+			100
22	15	100	+		+++	
23	Increase	95	±		+++	
24	80	95		36		44
25	50	100	±			62
26	45	75	++			76
27	5	100		38		74
28	90	100		23		104
29	5	100		14		28
30	10	100		43		59
31	40	90		50		96
32	65	100		23		77
33	90	98		34		74
34	500	100	±		+++	
35	200	100		37		77
36	10	100		25		96
37	3	100		29		190
38	85	100		25		60
39	4	100		19		89
40	Increase	Increase		174		93
41	80	40		58		46
42	30	100		26		67
43	20	100		36		67
44	12	100		30		76
45	5	100	±			70
46	0	0	±			69
47	15	100		60		77
48	24	100		24		99
49	19	100		15		46
50	Spinal tap not done					
51	90	60	+			52
52	0	0		14		87
53	7	100	±			63
54	340	99		49		61
55	225	70		24		63
56	380	100		32		72
57	10	100		30		84
58	75	90		33		81
59	3	100		19		74

* The ± sign indicates normal, + a slight increase, ++ a moderate increase

† The +++ sign indicates normal

others. These observations indicate that while in most instances the neurologic pattern is well defined at the time of discharge, on occasion significant changes in the patient's status may occur with the passage of time.

TABLE IV
FOLLOW-UP FINDINGS IN THIRTY-THREE CASES OF VARICELLA ENCEPHALITIS

	No. of Cases
No abnormality	23
Mental retardation	3
Personality change	2
Hemiparesis	2
Paresis of one extremity	1
Paralysis of both legs	1
Recurring convulsions	1
Blindness	1
Speech disturbance	1

Prognosis. Although a favorable outcome may be anticipated in the vast majority of cases of varicella encephalitis, the prognosis should nevertheless be guarded. Hyperpyrexia, which occurred in only one of the three fatal cases, could not necessarily be regarded as an unfavorable sign. Age seemed to bear no relation to prognosis. Little if any prognostic significance could be attached to the facts that the three deaths were in males and that most of the patients with residua were males, since 70 per cent of the patients in this series were males. The spinal fluid findings were of no aid in prognosis. We were unable to find any correlation between the severity of the encephalitis and the time of its development in relation to the rash. The presence of an added complication, particularly pneumonia, appeared to be an unfavorable prognostic factor. This was noted in two of the fatal cases. The occurrence of stupor did not necessarily indicate a poor prognosis. Onset with convulsions was, in most instances, an ominous prognostic sign. The intensity of the encephalitis seemed unrelated to the severity of the varicella.

TABLE V
NEUROLOGIC CHANGES SUBSEQUENT TO DISCHARGE FROM THE HOSPITAL IN THIRTY-THREE FOLLOWED-UP CASES OF VARICELLA ENCEPHALITIS

Condition on Discharge	Number of Cases	Number with Sequelae on Follow-up	Number without Sequelae on Follow-up	Time Since Discharge When Changes Were Noted
Without residua	24	3	21	6 mo. in two cases; 3 yr. in one case
With residua	9	7*	2	1 yr. in one case; 3 yr. in one case
Total	33	10	23	

* Two cases showed partial clearing of residua at end of two years

Treatment. No specific therapy was employed. The use of antibiotics in the more recent cases did not appear to alter the course of the illness. In this connection it may be of interest to call attention to recent studies of Kabat et al.[24] and of Moyer and his co-workers[25] which show that experimental demyelinating encephalomyelitis can be suppressed by the use of either corticotropin or cortisone. In the light of these studies it would seem worth while to investigate the clinical use of these hormones in the early phase of varicella encephalitis.

SUMMARY AND CONCLUSIONS

1. This report summarizes the experience with fifty-nine cases of varicella encephalitis seen at the Willard Parker Hospital from 1938 to 1952 and by the Division of Acute Infections of the Central Nervous System of the New York City Health Department from 1931 to 1951.

2. The pathology is discussed on the basis of six cases from the literature. The consistent histologic findings in these cases were perivascular cellular infiltration and damage to the myelin. The latter was not found in the one necropsied case in this series.

3. The clinical manifestations are described. The onset most commonly occurs between the third and the eighth posteruptive days. In a majority of the cases the clinical picture reflects an acute meningoencephalitic insult, with fever, change in the sensorium and signs of meningeal irritation and in some instances with convulsions and paralysis as well. The clinical course is variable, and almost any sign and symptom indicative of involvement of the central nervous system may be encountered.

4. The spinal fluid was usually clear, with an increase in cells, predominantly lymphocytes. An increase in the protein content was noted in slightly more than half of the cases. The sugar content was generally normal and cultures were sterile.

5. The mortality rate in this series was 5 per cent. The vast majority of the patients escaped

without sequelae. While in most instances the neurologic pattern was well defined at the time of discharge, on occasion significant changes in the patient's status occurred with the passage of time.

6. Prognostic factors are discussed. Although a favorable outcome may be anticipated in the vast majority of cases of varicella encephalitis, the prognosis should nevertheless be guarded.

7. Treatment was entirely symptomatic. The use of hormonal therapy requires investigation.

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Seminars on Neuromuscular Physiology

Some Aspects of the Pharmacology of Neuromuscular Function*

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IN any discussion on the pharmacology of neuromuscular function, acetylcholine (ACh) (Fig. 5) must serve as a focal point. The reasons for this are: (1) ACh release has been shown to follow motor nerve stimulation;[1] (2) ACh has been defined clearly to initiate excitation at the neuromuscular junction (n.m.j.) with singular specificity;[2] (3) ACh, as a naturally occurring quaternary amine, serves as a prototype for numerous synthetic quaternary ammonium substances. Therefore, the several effects of ACh on the n.m.j. will be outlined first and later the actions of other substances referred to this basis.

FIG. 1. The response of striated muscle to the intra-arterial injection of ACh. Isometric myogram and action potentials from cat gastrocnemius muscle; ACh 25 μ injected intra-arterially; time interval: 10 msec.; note the repetitive electrical activity. (After BROWN. *J. Physiol.*, 89: 220, 1937.)

ACTION OF ACh ON THE NEUROMUSCULAR APPARATUS

Among the number of effects that a compound may have on the neuromuscular synapse, the most simple and obvious one is the production of muscle contraction. It is a well established fact that mammalian striated muscle responds to the application of ACh with a contractile effect. However, it is noteworthy that the appreciation of this effect was considerably delayed because of the failure to administer the ACh properly in the experimental animal. In the intact mammalian preparation, including man, it is essential that ACh be given directly into the arterial supply of the muscle under observation if a pharmacologic effect is to be obtained.[3–5] The technic of close intra-arterial injection, now widely employed, was first described by Brown et al.[3] who found that the mechanically recorded contractile response to ACh superficially resembled the twitch response to a single maximal nerve shock. However, on further study[6] he showed with electrical recording that the ACh contraction is not simple, but is in fact a brief asynchronous tetanus. The nature of this effect is illustrated in Figure 1. Rather than a single action potential, there occurs a series of repetitive potentials, indicative of a summated mechanical response. The initial

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frequency of the discharge set off by ACh may be as high as 200/sec., but this decays rapidly and the entire effect is exceedingly brief, lasting perhaps for little more than a second. It is pertinent to ask why the intravenous administration of ACh, even in large doses, does not result in a contractile response of skeletal muscle. This lack of effect of ACh may be attributed in part to the partial hydrolysis of the ester by the cholinesterases (ChE) of the blood and tissues, but a more important reason is undoubtedly the fact that this mode of administration does not result in the achievement of a temporally uniform activating concentration of ACh at the several motor end plates within any given muscle.[7] This relates directly to the extreme brevity of ACh action at the n.m.j.

The action of ACh on striated muscle has been classified as a nicotine-like response, but more important than the classification of this action of ACh as nicotinic is the role that nicotine has played in the localization of the ACh effect. Considerably before the recognition of ACh as a compound of either physiologic or pharmacologic importance, Langley[8] with the use of nicotine distinguished the specialized receptor area of striated muscle. This he accomplished by applying certain concentrations of nicotine base to various sites along the isolated frog sartorius muscle. Discrete application of the alkaloid was achieved by means of a fine hair and it was shown that the muscle responded to small concentrations of nicotine only when this substance was applied at the site of the nerve entry. It was many years later that other workers,[9,10] utilizing the technic of microapplication in conjuncture with electrical recording, were able to demonstrate a similar fact for ACh. In one of these experiments, ACh was applied directly to the motor end plate of a fiber from the internal thoracic muscle of the lizard.[9] The effect produced was like that of a brief high-frequency tetanus. Kuffler reported that the application of ACh to the end plate region of the frog sartorius muscle resulted in the propagation of a series of electrical responses.[10] The important observation was made in this experiment that despite continued exposure to ACh, the discharge from the motor end plate did not continue, and it was concluded that some adaptive capacity on the part of the end plate membrane enabled adjustment to prolonged exposure to the quaternary ammonium ion. It was also noted that as much as 1,000 times the threshold concentration of ACh applied other than at the end plate produced at most only a small local contracture. For mammalian muscle, the localization of ACh action to the motor end plate was achieved more recently by the ingenious experiment of Burns and Paton.[11] These workers used a continuously moving electrode that explored the entire surface of the intact gracilis muscle of the cat. In this circumstance the close intra-arterial injection of a small amount of ACh produced an immediate and considerable depolarization of the end plate region only. Some slight spread of the depolarization process from the end plate region was detected and this could be accentuated by the prior inactivation of ChE. Depolarization spread was attributed to involvement of muscle membrane adjacent to the depolarized end plate. The important point was demonstrated that the intensity of end plate depolarization is dependent on the local concentration of ACh. Thus if sufficiently large doses of ACh were administered after the inactivation of ChE, the end plate region became depolarized to an extent at which it was no longer responsive to indirect stimuli. When neuromuscular transmission was disrupted by a persistent depolarizing agent, it was possible to restore transmission by the application of anodal current to the strongly depolarized end plate locus.[11] The effect of ACh on the motor end plate, then, is like that of a strong cathodal current.

A major contribution to the physiology of neuromuscular transmission was made by the researches of Eccles and his collaborators[12,13] wherein they defined the response of the motor end plate to a nerve impulse and the role of the end plate in the creation of the propagated action current. Briefly, it was found that the end plate generated a localized non-propagated potential in response to the nerve stimulus, and that when the magnitude of this potential reached a certain critical value, a superimposed spike appeared at the peak of the end plate potential and traversed the remainder of the muscle. The consideration of ACh as the humoral transmitter of the nervous impulse demands that a similar demonstration be made for the effect of ACh on the motor end plate. In the foregoing paragraph the activation of the motor end plate region by ACh has been summarized, and in this activation the precedent formation of an end plate potential is implicit.

Appropriately, Kuffler[10] was able to show that when sub-threshold concentrations of ACh were applied at the motor end plate of the frog sartorius fiber, there occurred a localized non-propagated potential. Recently Nastuk[14] has attempted to simulate the neural release of ACh by transitory application with a microjet. The jet was directed at the surface of an individual end plate of frog striated muscle, and its duration was adjusted to one msec. Increasing amounts of ACh successively produced responses at first resembling pure end plate potentials, and then end plate potentials large enough to initiate one or more propagated action potentials. Application elsewhere on the fiber was ineffective. In this way the unique specificity of ACh at the end plate region was once again confirmed.

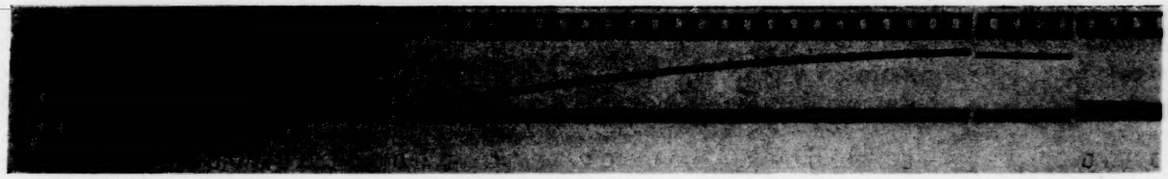


FIG. 2. The response of denervated striated muscle to ACh. Myogram and action potentials from cat gastrocnemius eleven days after sciatic nerve section; ACh 2.5 μ injected intra-arterially; time interval: 10 msec. (After BROWN. *J. Physiol.*, 89: 438, 1937.)

Through the studies of Dale and Gasser[15] the unusually high sensitivity of chronically denervated mammalian muscle to ACh was first recognized. In fact, the description of the contractile response of denervated muscle to ACh preceded by several years the discovery of this effect in the normally innervated or acutely denervated structure. With the technic of close intra-arterial injection, Brown et al.[3] revealed that the chronically denervated gastrocnemius muscle of the cat responded to as little as 0.001 μg. of ACh. With suitably large doses, the mechanical response of this muscle was shown to consist of an initial quick contraction followed by a prolonged contracture. (Fig. 2.) Accompanying electrical recording (Fig. 2) made it evident that the quick phase of the contraction was preceded by a burst of propagated action potentials, like that which occur in normal muscle, but that the secondary slow contracture was associated with electrical silence. It is perhaps significant that following an initial dose of ACh the reactivity to a subsequent dose is depressed, if it is given during the period in which electrical activity is suppressed. In this period contracture may result from the ACh administration, but the quick component associated with an action potential is not evoked. It is possible that the repolarization process in chronically denervated muscle is retarded, and that the slow component of contraction does not originate at the end plate. As in the normal muscle the initiation of the response to ACh has been localized to the region of the motor end plate.[10]

CHEMICAL DETERMINANTS OF THE ACTIVITY OF ACh AND RELATED IONS AT THE N.M.J.

While the physiologist concerns himself primarily with the definition of those biophysical components that operate in an integrated fashion to effect neuromuscular transmission and muscle contraction, the pharmacologist has the opportunity to examine the chemical characteristics of the system. Such an approach will furnish not only pharmacologic information but will also provide details on the chemical specificity and reactivity of the cellular structures in question. To this end the chemical characterization of ACh as an alkyl quaternary ammonium salt immediately furnishes the fact that this substance is one of a distinctive class of organic compounds typified by a strong basicity. The importance of this ionic character in the pharmacologic action of these compounds is unequivocal. In fact, the weight of evidence now indicates that the initiation of excitation at the motor end plate by ACh is a consequence of an electrostatic interaction between the quaternary ammonium ion and some oppositely charged ion of the end plate receptor.

In 1931 Ing and Wright[16] first entertained the idea that the bond between simple mono-quaternary salts and the neuromuscular receptor may be ionic in type. This hypothesis was based on the consideration of the chemical characteristics of the quaternary alkyl onium ion as contrasted with those of the tertiary amine. The principal chemical difference is the achievement of the maximum covalency of the nitrogen atom through union with carbon

atoms. (Fig. 3.) This produces a stability not found in the cations of other amine salts. The cation of a tertiary amine may be represented as: R_3NH^+. This will react with hydroxyl ion as follows: $R_3NH^+ + OH^- \rightleftarrows R_3N + H_2O$. Thus in contrast to the stability of the quaternary ammonium base, the tertiary base does not retain a positive charge at alkaline or physiologic pH.[17]

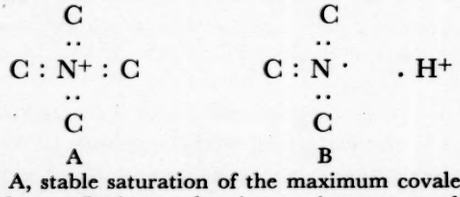


FIG. 3. A, stable saturation of the maximum covalency of the N atom; B, the covalent ionogenic structure of the tertiary amine.

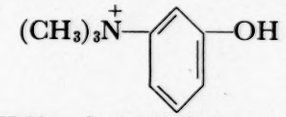
This stability of the quaternary ammonium cation leaves little likelihood for its decomposition in the tissues. The rapidity of the reaction of quaternary ammonium salts with the n.m.j. led Ing and Wright to suspect that the preliminary binding of the salt was a function of its ionic nature, but that some secondary slower process completed the reaction. As a suggestion, the possibility was put forth that the binding might be likened to some type of ionic exchange or permutit-like reaction in which the onium ion replaced some normal cation in the membrane. However, equally significant in the data was the finding on the frog sartorius preparation that the tertiary amine, trimethylamine oxide, retained only a trace of the pharmacologic activity of the tetramethylammonium ion. This accords with the loss of ionic charge by the tertiary amine at alkaline pH as formulated above. Also consistent with this idea was the additional finding that NH_4Cl possessed only a feeble action on the nerve muscle preparation and that its effect was transient. Hence, the slight pharmacologic activities of trimethylamine oxide and NH_4Cl provide further evidence for the importance of strong ionic character in the achievement of a depolarizing effect.

The analogy between the alkyl trimethylammonium ions and alkali metal ions was considered in detail by Alles and Knoefel.[18] Pharmacologically the chief difference between the two ion types is a quantitative one: the alkali metal ions possessed from 1/100th to 1/1000th the potency of the alkyl trimethylammonium salts when these were compared on various systems. Both ion series exhibited differences within their particular series; for the alkali metals, K^+ was most active and for the alkyl trimethylammonium series, maximal activity appeared in the butyl and amyl derivatives. To interpret the maximum reactivity of certain members of both series, receptor specificity may be assumed. For the alkyl trimethylammonium series, Alles and Knoefel postulated that the limiting factor in receptor fit was molecular dimension. The apparent discrepancy between K^+ and alkyl trimethylammonium ion was explained by considering the K^+ ion to be hydrated in solution and in this way the volume of ions like K^+ and Rb^+ were shown to correspond closely with that of the tetramethylammonium ion. From this it was concluded that the similar pharmacologic action of each ion type could be attributed to size. However, in view of more recent deliberations[2,19,20] on the mechanism of pharmacologic activity of quaternary ammonium salts, the more important factor appears to be the magnitude of the ionic charge. Furthermore, it is a fact that the size of an ion or ionic head is secondary since ionic size relates directly to the nuclear charge. For example, the greater the nuclear charge the smaller will be the ionic size in view of the greater pull on the outermost orbital electrons. Thus in the achievement of an electrostatic interaction, closest possible approach of the two oppositely charged centers will be influenced by the ionic radii.

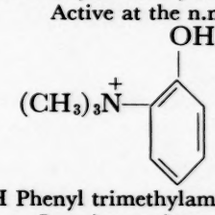
The contractile reaction of amphibian and mammalian striated muscle to K^+ has long been known.[21,22] In addition to producing contractile responses in mammalian muscle, both chronically and acutely denervated, K^+ injected intra-arterially into the mammalian or amphibian neuromuscular preparation, responding to single maximal nerve shocks, increases the tension of the response just as ACh does[22,23] although the action of K^+ is longer lasting than that of ACh. Also like ACh, K^+ in excess produces a depression of the indirectly evoked response.[22,23] This may be attributed to the reduction of the resting and end plate potentials.[23] In another respect K^+ resembles ACh and related quaternary ammonium ions in that it is able to antagonize the action of curare.[22] In the curarized frog muscle the effect of K^+ on the motor end plate is like that which follows exposure to anti-ChE agents; the end plate potential is first increased and restoration of transmission follows.[24] However, the anti-curare action of K^+ differs in one

important particular, in that transmission eventually fails, despite the fact that the end plate potential remains at an adequate level. This is due to the indiscriminate depolarizing action of K^+; as a consequence, the muscle membrane other than at the end plate becomes affected and propagation is impaired. This non-specific depolarizing action of K^+ contrasts with the specific depolarization of the end plate produced by ACh.[10] It is possible that this difference in specificity between the ionic actions of quaternary ammonium salts and K^+ relates to the fact that the latter ion readily penetrates the cell membrane whereas the quaternary ammonium ions do not.[17] The important point to be stressed in summary is that the quaternary ammonium salts, especially ACh, have ionic properties similar to K^+ and both ion types are capable of initiating excitation, paralyzing neuromuscular transmission and antagonizing curare at the motor end plate.

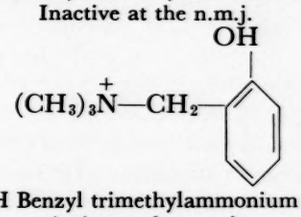
The critical significance of ionic charge for the completion of the reaction between a quaternary ammonium salt and the receptor of the n.m.j. may be appreciated from those experiments in which the state of the ionic charge has been influenced or modified in some way by chemical alteration of the molecule. The earliest evidence that the acquisition of an ionic charge evolves an affinity for the n.m.j., for a group of drugs not ordinarily possessing this pharmacologic property, dates back to 1869. In that year Crum-Brown and Fraser[25] converted the tertiary bases of brucine, thebaine, codeine, morphine, etc., into quaternary methyl salts. These quaternary salts were shown to have developed a new pharmacologic action in that their administration was followed by paralysis of the voluntary musculature. In opposite fashion it has been possible to illustrate the loss of this affinity for the n.m.j. when the effect of the ionic charge is nullified or reduced. This has been done in a molecule like betaine which is, in fact, a double ion. The acid radical adjacent to the charged onium center effectively neutralizes the influence of the charge and, as a result, this simple quaternary ammonium structure is without excitatory action on the motor end plate.[26] The internal neutralization of charge as illustrated by betaine is more subtly manifested in other compounds. For example, 3-OH phenyltrimethylammonium ion exerts a prominent excitatory action on the mammalian n.m.j.[27,29] This action can be virtually abolished by the removal of the OH grouping from the 3 position to the 2 position as shown in Figure 4.[27–29] This is equivalent to the impedance of an organic reaction by the proximity of an indifferent group to the reacting group of a molecule; it is referred to as the proximity or



3-OH Phenyl trimethylammonium ion
Active at the n.m.j.



2-OH Phenyl trimethylammonium ion
Inactive at the n.m.j.



2-OH Benzyl trimethylammonium ion
Active at the n.m.j.

FIG. 4.

ortho effect. The effect may be due to direct steric hindrance or it may arise from the proximity of oppositely charged centers with consequent direct field neutralization. For the 2-OH phenyltrimethylammonium ion the latter situation probably prevails, thus preventing the ionic reaction of the quaternary ammonium center with the receptor. That the 2 position *per se* does not impair the reactivity of the onium salt is evident from the fact that the proper separation of the OH group from the onium center by the insertion of a methylene group, to form 2-OH benzyltrimethylammonium ion, restores the pharmacologic potency of the compound.[29] (Fig. 4.) Thus it is apparent that the charged onium center must remain unimpeded if reaction with the receptor is to be accomplished.

The concept of the strength of ionic charge as a determinant in the reaction of a quaternary ammonium salt with the neuromuscular receptor has been introduced recently by Holmes et al.[19] The postulation was made that in an ion, such as R_4N^+, the distribution of charge will depend on the relative electronegativity of the substituent group. On this predication, the simple alkylonium ions, tetramethyl-, tetraethyl-, tetra-

propyl-, and tetrabutylammonium were examined for their relative paralyzing activities on a frog muscle preparation. The relative electronegativities of the substituent groups were obtained from the evaluation of the dissociation constants of the corresponding car-

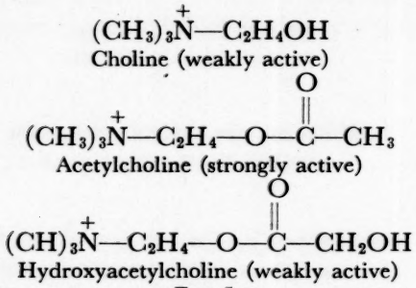


FIG. 5.

boxylic acids as well as the dissociation constants of the mono-, di-, and tri-substituted amines. Paralyzing activity was seen to parallel the effectiveness of the charge on the central onium atom. The least active in the series was tetraethylammonium ion and in this compound the charge was most dispersed. In this regard the ethyl group is anomalous and Taylor[20] has commented on the fact that a similar irregularity has been described for the behavior of ethyl compounds in certain organic reactions. No adequate explanation for the odd polarity of the ethyl group is yet available. From these considerations it is probable that ethonium structures lack a significant depolarizing action on the n.m.j. because of excessive dispersion of charge. The literature contains numerous examples that disclose the loss or diminution of depolarizing capacity that occurs when ethyl groups replace methyl groups attached to the nitrogen atom.[2] Chief among these examples is the loss of activity that results when two or more of the methyl groups in the tetramethylammonium structure are replaced by ethyl groups. The influence of an ethyl-methyl interchange is also apparent with the 3-OH phenyltrimethylammonium ion. In this circumstance the successive substitution of the methyl groups by ethyl groups leads to a progressive decline in the activity of this compound at the n.m.j. When one of these methyl groups is replaced by an ethyl group, there is only slight loss in potency; this compound, 3-OH phenyldimethylethylammonium bromide, is available commercially as an anti-curare agent (tensilon®). However, when two of the methyl groups are supplanted by ethyl groups there is a profound loss in excitatory action on the n.m.j. and the replacement of the third methyl group abolishes activity. For the trimethylphenylammonium ion, similar chemical alterations have been demonstrated to result in parallel changes in the pharmacologic properties.

While it has been seen that ionic size is secondary to the ionic charge as a determinant in the reaction between the ionic head of the molecule and the receptor, the over-all molecular dimensions are considerate factors in the fit that the drug makes with the receptor. To evaluate the influence of molecular size on the reactivity of the cationic head, the simplest procedure is to study the excitatory properties of the various n-alkyl trimethylammonium derivatives. This has been determined thoroughly with frog muscle preparations, but it remains to be done for the mammalian n.m.j. The results of the studies with frog muscle reveal that maximum excitatory activity appears when the alkyl chain consists of three or four carbon atoms.[18,30–32] When the chain length exceeds five carbon atoms, pharmacologic activity diminishes sharply. Extinction of activity is approached with the octyl derivative. It is significant that ACh itself consists of a chain of five atoms attached to the onium center. When this chain is lengthened or shortened through esterification of choline with other acids in the series, excitatory action decreases.[33] From these results it appears that the n.m.j. like other cholinergic receptors responds to a critical size factor in its reaction with quaternary ammonium bases.[34]

Another factor that has been seen recently to influence the reactivity of the cationic head of quaternary ammonium compounds is the presence of either an alcoholic hydroxyl or a phenolic hydroxyl grouping. It has long been known that the general pharmacologic reactivity of choline is only a fraction of that of the acetyl ester of this substance.[15,33,35–37] For the mammalian n.m.j. Bacq and Brown[33] estimated that choline had only approximately 1/1000th the excitatory activity of ACh. The fact that esterification increased the potency of a base like choline was recognized through the fact that esterification with acids such as propionic, butyric and formic achieved this effect, although not to the same degree that resulted when esterification was made with acetic acid. The reason for the effect of esterification has been

obscure. However, certain facts appear to implicate the OH grouping as having a detrimental effect on the reactivity of a quaternary ammonium base. Essentially, esterification may be a procedure that accomplishes the masking of a polar OH group. For example, the compound ethyl trimethylammonium ion is a more potent agent on frog muscle than is choline, the two compounds differing only by an hydroxyl group.[31,37] Another significant fact that has been in the literature for a considerable period discloses that the introduction of an hydroxyl group onto the terminal carbon atom of ACh (hydroxyacetylcholine; Fig. 5) virtually annuls the increase in excitatory action that might be expected to follow esterification.[37] This sharp difference between ACh and hydroxyacetylcholine indicates that esterification *per se* does not account entirely for the increase in excitatory activity, since the reintroduction of a terminal hydroxyl group serves to destroy the usual effect. The most likely explanation for the effect of an OH group is the tendency of this grouping to associate with the similar groups of the aqueous milieu through hydrogen bonding. The net effect of this would be to retard the close approach of the cationic head toward an anionic locus on the receptor.

The effect of an hydroxyl group is less deleterious when it is attached to an aromatic ring substituent of an onium cation. Unlike choline, the excitatory activity of 3-OH phenyltrimethylammonium ion at the n.m.j. is strong, but it is slightly less potent than the phenyltrimethylammonium ion.[27,38,39] The lesser influence of the phenolic hydroxyl as opposed to an alcoholic hydroxyl on excitatory activity may be attributed to the influence of the ring structure. From the early work of Hunt and Taveau[35] on quaternary ammonium substances it has been recognized that the nicotine-like properties of these materials are most prominent when an aromatic ring is part of the molecule. This is particularly true for the n.m.j. when the ring is attached to the onium atom.[27,28] The cyclic structure may reinforce the ionic interaction through non-specific cohesive forces developed between it and the receptor surface.

In considering the receptor specificity of a compound like ACh, factors such as ionic charge, chain length and substituent groupings in the side chain have been discussed. There remains, however, the fact that the onset, duration and elimination of ACh action at the n.m.j., when viewed as an entity is unique among quaternary ammonium compounds. Contributory to this specificity there remains for consideration only the carbonyl grouping of the ester link. It is a well recognized fact that resonance of this

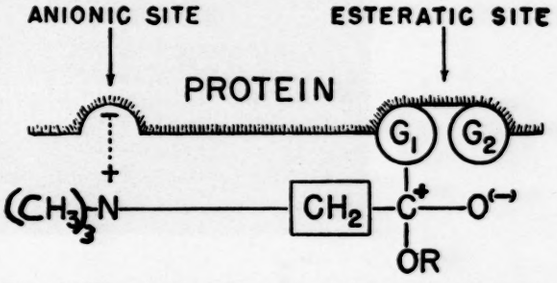


FIG. 6. Hypothetical diagram of interaction between the active groups of ACh and ChE. G_1 and G_2 are, respectively, adjacent negative and positive charges. (After WILSON and BERGMANN. *J. Biol. Chem.*, 186: 683, 1950.)

grouping occurs and as a consequence the reactivity of the carbonyl carbon atom will be increased by its relative positivity, as noted by Wilson and Bergmann[40,41] for the reaction between ACh and purified ChE. (Fig. 6.) Furthermore, the oxygen atom of the carbonyl group may react with some positively charged ion in the receptor. Thus the initial ionic interaction of the cationic head of ACh with some oppositely charged group in the receptor molecule may be supported by a secondary reaction of the carbonyl grouping with some appropriately spaced site on the receptor molecule. In this way an optimal union between drug and receptor may be achieved.

The postulates of Wilson and Bergmann, founded on the mechanism of alkaline ester hydrolysis, propose that the reaction between ChE and ACh culminates in the hydrolysis of ACh because of the activation of the ester link that occurs from the union of the carbonyl carbon atom with some moiety of the enzyme. (Fig. 6.) It is highly probable that such an attachment between ACh and the receptor would similarly lead to an activation of the ester link followed by hydrolysis of the ester. On this basis the ensuing liberation of a terminal hydroxyl group would again serve to weaken the ionic binding, as previously defined, and pharmacologic activity would thereby be terminated. If this assumption were true, the receptor of the n.m.j. would simultaneously possess esterasic activity and ChE and receptor

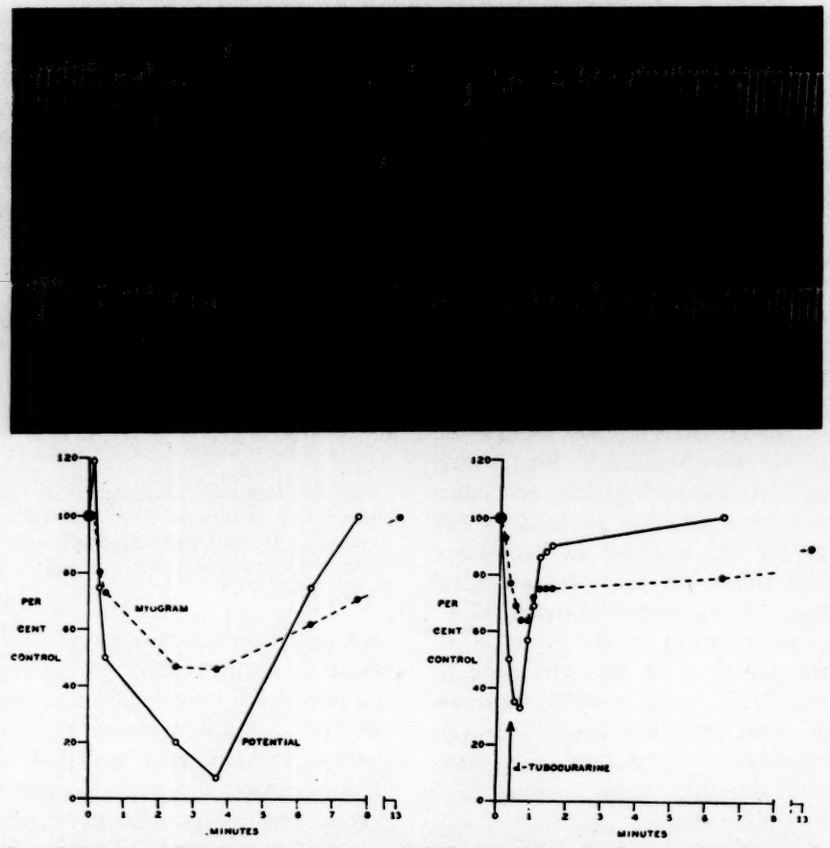


FIG. 7. Reciprocal antagonism between 3-OH phenyltrimethylammonium ion and curare in the cat. The spinal cord was sectioned at C1 and positive pressure artificial respiration applied through a tracheal cannula. In the upper tracing, the paralyzing effect of a large intravenous dose of 3-OH phenyltrimethylammonium ion is recorded. Lower tracing: sixty minutes later, repetition of the 3-OH phenyltrimethylammonium dose is followed within twenty seconds by an intravenous dose of d-tubocurarine. Note the effect of curare to abort the paralysis. The graphs below plot the time course of neuromuscular depression and recovery in each instance, determined from the myograms and simultaneously recorded action potentials. The left and right graphs, respectively, refer to the upper and lower tracings. (After RIKER and WESCOE. *J. Pharmacol. & Exper. Therap.*, 100: 454, 1950.)

at this site would be identical. The reaction of ACh with ChE *in vitro* may serve as a model for the reaction of ACh with the cell receptor *in vivo*.[42]

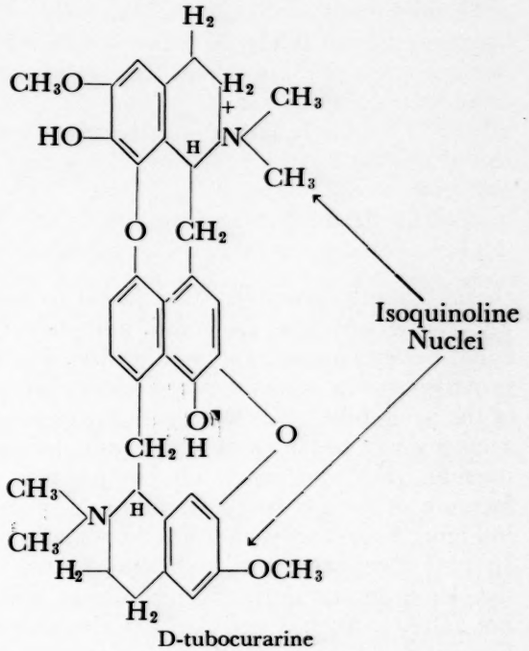
BLOCKADE OF NEUROMUSCULAR TRANSMISSION BY EXCESSIVE DEPOLARIZATION

The recognition of the disruption of neuromuscular transmission by quaternary ammonium ions dates back to 1869.[25] In the early part of this century Boehm[43] and Marshall[44,45] each demonstrated the paralytic actions of the tetramethylammonium ion and other quaternary ammonium bases. For the alkyl trimethylammonium series, methyl through octyl, the paralyzing activity on the frog nerve muscle preparation has been described by several workers.[17,31] Furthermore, the fact was noted that the paralyzing action of these compounds was associated with a capacity to excite contracture of the frog's rectus abdominis muscle. Some decades later, in conjunction with the recognition of the excitatory action of ACh on the mammalian n.m.j., it was also revealed that excessive amounts of ACh led to a depression of neuromuscular transmission. This condition was easily established if the esterasic activity was first diminished by an appropriate anti-ChE agent.[33] ACh then, like other simple quaternary ammonium bases, manifests this paralyzing action. For the mammalian neuro-

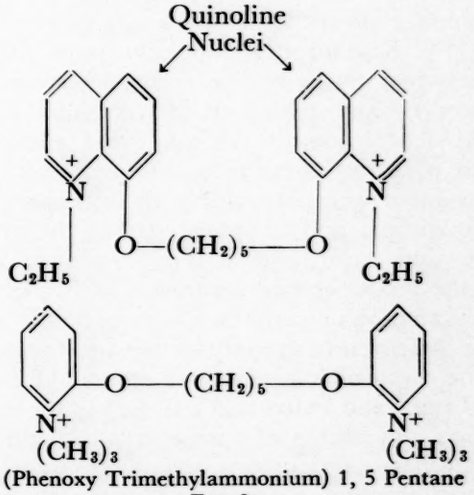
muscular preparation it becomes apparent that the paralyzing action of a quaternary ammonium base, such as ACh, is first preceded by an excitatory effect. In some cases this effect is exceedingly transient and paralysis quickly supervenes. With suitable exploration of dose range, it is possible to avoid paralyzing effects and to obtain only excitatory manifestations of quaternary ammonium action. This has been well demonstrated for the action of decamethonium bromide (C 10) on the n.m.j.[46]

The initiation of excitation in striated muscle depends on the achievement of a critical depolarization of the end plate membrane.[47] Similarly, it has been shown that when depolarization of the end plate region is excessive, it is no longer possible to generate an adequate end plate potential through nerve stimulation; but if polarization is restored by an applied anodal current, transmission is reestablished.[11] From this and the foregoing evidence it is clear that the quaternary ammonium blockade of neuromuscular transmission is the equivalent of a cathodal block. The pharmacologic counterpart of these events is represented by the mutual antagonism that exists between curare and a quaternary ammonium salt that has strong excitatory actions on the n.m.j., e.g., 3-OH phenyltrimethylammonium bromide.[28] While the antagonism of curare by 3-OH phenyl trimethylammonium ion is readily demonstrable, the reverse action is not so easily revealed. For the antagonistic drugs the balance of concentrations at the motor end plate necessary to allow transmission of the nerve impulse to proceed normally is a delicate one. Either a slight excess of curare or a slight excess of quaternary ammonium ion will serve to depress transmission by either one of the two contrasting mechanisms. This aspect of the mutual antagonism between curare and 3-OH phenyltrimethylammonium ion is exhibited in Figure 7. In this circumstance then, curare acts to restore transmission and is equivalent in effect to the application of anodal current; it acts to impede the depolarization of the end plate[48] and in this sense may be said to be a "membrane stabilizer." Unfortunately, the frequent failure to recognize the two opposite means by which curare and ACh-like substances depress neuromuscular function has resulted in the indiscriminate use of the terms, curarizing and curariform. From the etymologic standpoint these terms should be restricted to those agents disrupting neuromuscular transmission by an action demonstrably like that of curare.

Advances in our knowledge often appear to have developed in orderly sequence; but when the actual occurrences that have led to an advance are seen in retrospect, one realizes that



D-tubocurarine



Bis (Phenoxy Trimethylammonium) 1, 5 Pentane

FIG. 8.

a priori reasoning is frequently awry. This has been the case in part in the development of synthetic paralyzing agents. The first attempts to duplicate synthetically the action of the natural alkaloid curare were made by Bovet and his collaborators in 1946.[49] In this work they used as a model the recently defined

formula of d-tubocurarine[50] (Fig. 8) and recognized as an important feature the twinning of isoquinoline nuclei through ether linkages. With this as a basis, they prepared bis-quinoline derivatives wherein the ring structures were connected through ether links by a methylene chain. These compounds were found to exert a paralyzing action at the n.m.j. and this action could be antagonized by neostigmine. This fact provides strong presumptive evidence in favor of the probability that these substances produce a curariform paralysis of neuromuscular transmission. For purposes of comparison, the formula of such a synthetic material is shown in Figure 8 together with that of d-tubocurarine. In 1947 these same workers[51] showed that even simpler aromatic derivatives exhibited curarizing activity. Such a derivative is also shown in Figure 8 wherein two phenoxytrimethylammonium ions are joined by a methylene chain. In 1949 Kimura et al.[52] demonstrated the fact that when two atropine molecules were connected through their nitrogen atoms by a polymethylene bridge, there resulted a compound with a strong paralyzing action. All of these substances were susceptible to antagonism by neostigmine, and it appeared that the prediction that curariform activity depended solely on the proper spatial separation of two quaternary ammonium groups was remarkably accurate. Attempts to simplify further what appeared to be the principle of curare action led Barlow and Ing[53] and Paton and Zaimis[54] to the preparation and testing of compounds in which the quaternary ammonium structures were connected through a simple methylene chain. In accord with expectations, a potent neuromuscular paralyzing action was manifest when the proper spatial separation of the onium groups was achieved. However, Paton and Zaimis quickly discerned features of the blockade that were unlike the characteristics of curare paralysis. Chief among these differences were: (1) the lack of antagonism by neostigmine; (2) the intensification of the block by neostigmine; (3) the antagonism of the bis methonium compound by curare. In a subsequent study[11] earlier suspicions were confirmed when it was ascertained that the decamethylene bis onium compound C 10 (Fig. 9), like ACh, depolarized

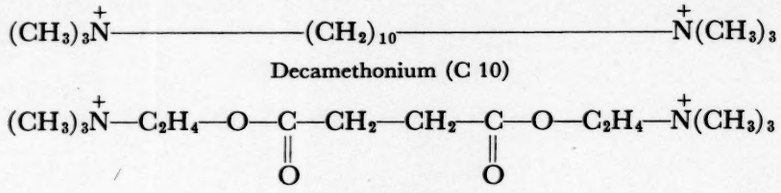


FIG. 9.

the end plate region in cat striated muscle. The intensity and duration of the depolarization was a function of the dose and in turn determined the degree of paralysis observed. Thus the manner in which the quaternary ammonium functions are disposed makes a considerable difference in the quality of the action that is elicited. In view of the fact that this type of blockade represents a depolarizing action, it will be realized that the means usually employed to antagonize curare will not be effective in this circumstance. Thus physostigmine, neostigmine or other anti-ChE substances will only serve to intensify the blockade produced by C 10. Tensilon, having an ACh-like action, will also be contraindicated in the presence of C 10. From the practical standpoint, there is little to be done to alleviate the quaternary ammonium blockade produced by depolarizing substances like C 10 or succinylcholine. In the presence of respiratory embarrassment it will be essential to maintain an adequate airway and to administer controlled respiration. Paton and Zaimis[54] found for the cat that the action of C 10 could be antagonized partly by C 5, but this type of competitive interaction does not occur in man. Recently, de Beer et al.[55] reported a bis quaternary ammonium compound capable of antagonizing the quaternary ammonium type of block produced by C 10 and succinylcholine. In the dose employed to produce the antagonism, the compound by itself had no evident action. Apparently competitive displacement is involved here. Although the effectiveness of this substance in man has been reported in a preliminary trial,[56] more extensive clinical and pharmacologic information is needed.

While the alkyl trimethylammonium ions

were of considerable academic import, the paralysis produced by suitable doses of these agents was never of any practical significance. It was not until the recognition of the intense depolarizing action of certain of the polymethylene bis quaternary amines that practical interest developed. Consequently, academic concern with the mechanism of quaternary ammonium blockade was renewed. For these compounds it was found that paralyzing activity varied depending on the distance by which the quaternary ammonium groups were separated; maximal activity appeared when the connecting chain consisted of ten methylene groups.[53,54] Similarly, Bovet et al.[57] accomplished an equivalent separation of two quaternary ammonium groups through the bis esterification of dicarboxylic acids with choline. Most active among this series was the bis choline ester of succinic acid (succinylcholine). (Fig. 9.) On inspection of the formula it becomes apparent that succinylcholine is in fact a union of two ACh molecules through their terminal methyl groups. The reason for the potent depolarizing action of drugs like C 10, succinylcholine and other aliphatic bis trimethylammonium derivatives remains uncertain, but it is noteworthy that these compounds were developed through a preliminary consideration of the molecule of d-tubocurarine, from which it became apparent that the two quaternary ammonium groups in the natural alkaloid were separated by a distance approximating 15 Å.[52] It is a remarkable fact, therefore, that the duplication of this inter-quaternary distance in compounds like C 10 and succinylcholine resulted in substances whose paralyzing effects were established in a manner exactly opposite to that of the natural alkaloid. However, it is highly probable that the distance factor operates in the same critical way for both types of blocking agents. The most reasonable speculation is that the two quaternary ammonium groupings separated by about 15 Å occur at some optimal distance for a two point attachment to the receptor. In this regard it is also noteworthy that the distance separating the two reactive centers of ACh is about 7 Å;[58] presumably the two cationic heads of the bis onium compound could unite at two regularly recurring anionic sites on the receptor surface. Certainly in the case of C 10, the strongly charged polar groupings proffer ionic interaction with the receptor as the only evident consideration for the mechanism of reaction.

BLOCKADE OF NEUROMUSCULAR TRANSMISSION BY CURARE; THE ANTAGONISM OF CURARE

Unlike the muscle paralyzed by C 10, the muscle made refractory to stimulation through its nerve by d-tubocurarine may be said to be electrically normal.[11] At every point on its surface the membrane potential remains as in the resting muscle, and its direct electrical excitability is the same at all points on the fiber. The fact that the curarized muscle responds to a direct electrical stimulus coupled with the fact that the integrity of nerve function is unchanged[59] and that d-tubocurarine does not affect the liberation of ACh[1] led to the definition of curare action as being at the motor end plate. Further details of the action at the end plate were revealed by Eccles and his collaborators.[13] With the recognition of the end plate potential as a detonator action, a basis for the action of curare was established. It was found that curare diminished the height of the end plate potential. The important point pharmacologically is the progressive decrease produced by curare in the response of the end plate to the nerve impulse. (Fig. 10.) Although the end plate potential may be diminished, the innervated fiber may continue to contract normally. However, if the voltage of the end plate potential is reduced sufficiently, the response in that fiber disappears entirely. (Fig. 10*e*.) The effect of curare as observed on the contractile process appears as an all or nothing effect but actually there exists a dose-response relationship for the trigger mechanism. The basis for the cumulative effect of curare is clear: A concentration of curare may be present in the organism sufficient to depress the response of a multitude of end plates to an extent that does not prevent spike propagation; but if an amount of curare calculated to be non-paralytic in the normal animal is added, an abrupt and complete paralysis may result as a consequence of a further lowering of the end plate potentials.

The fact that d-tubocurarine blocks the response to injected ACh as well as to the nerve impulse not only further established the identity of these two forms of stimulation of the motor end plate, but suggested that curare prevented the depolarization of the end plate region by ACh. The work of several investigators with isolated nerve muscle preparations has confirmed this point.[9,10,48] Recently, Burns and Paton[11] demonstrated the prevention by d-

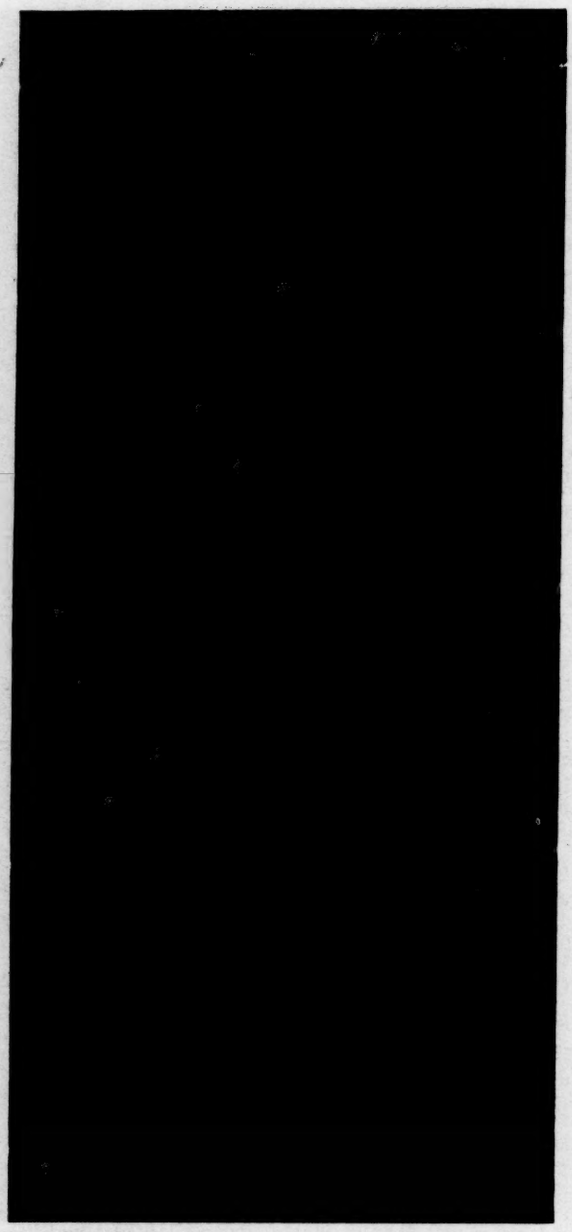


FIG. 10. The effect of curare on potentials recorded at the end plate; *a*, before curare; *b*, *c* and *d*, during progressive curarization. The end plate potential can be recognized as the step in the rising phase of the potential. From this point, the propagated action potential may be seen to arise. The effect of curare to lengthen progressively the origin of the action potential, increasingly diminish the end plate potential and eventually prevent spike development (*e*) can be readily noted. (After KUFFLER. *J. Neurophysiol.*, 5: 18, 1942.)

tubocurarine of the depolarization of the mammalian end plate region. On this basis then, antagonism of d-tubocurarine should occur when the depolarizing force is sufficiently strong to overcome the stabilization of the end plate membrane produced by the curare. Physiologically, this has been shown to happen when a strong cathodal pulse is applied to the end plate region.[48] Another example of this is the decurarizing effect that a strong tetanic stimulation exerts.[60,61] The weak effect of ACh as an anti-curare agent is presumably due to its extreme transience of action.[2] However, if this is prolonged, the intensity of its action is sufficient to overcome a d-tubocurarine blockade. In this way physostigmine and other anti-ChE compounds have proved efficient anti-curare agents. It is also possible to dissipate the blocking action of d-tubocurarine with synthetic quaternary ammonium compounds whose duration of action exceeds that of ACh. In this respect the permanent decurarizing action of 3-OH phenyltrimethylammonium ion has been described.[28] Presumably, the anti-ChE agents and the quaternary ammonium salts restore transmission by increasing the amplitude of the end plate potential in response to the nerve impulse. An excellent example of the antagonism of curare by a strong depolarizing agent is furnished by the anti-curare action of C 10.[62] The superior anti-curare action of neostigmine as compared with physostigmine[63,64] may be attributed to the fact that as a supplement to its anti-ChE properties it directly stimulates the motor end plate.

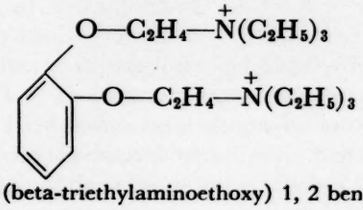
In addition to the antagonism of curare by direct excitatory activity at the motor end plate, it is also clear that the action of this alkaloid may be terminated by displacement. That this occurs and is a significant factor in the antagonism of curare has been realized through two types of experiment. Using the frog's rectus muscle, a tissue that gives a maintained response to ACh *in vitro*, it has been possible to show that the dose-response relationship to ACh is not altered in pattern by the presence of curare, but is simply shifted further along the dose abscissa. From this it was concluded that the antagonism between ACh and curare is competitive.[65] This conclusion has been confirmed by Kirschner and Stone[66] for curare as well as for related natural alkaloids.

CHEMICAL DETERMINANTS OF CURARIFORM ACTION

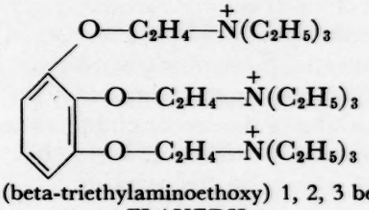
It perhaps appears contradictory that the natural alkaloid, d-tubocurarine, like C 10, possesses two quaternary ammonium nitrogens

separated by about 15 Å but has as a chief pharmacologic property the capacity to block neuromuscular transmission by preventing the depolarization of the motor end plate. It is probable that the lack of a depolarizing action of d-tubocurarine can be attributed to a reduction in the effective onium charge. This idea was suggested by Taylor[20] who considered the consequences on charge density when the nitrogen atoms are part of a ring structure as in d-tubocurarine. In this analysis the effective positive charge on the tertiary nitrogen atom of the isoquinoline ring was found to be reduced through resonance within the ring structure and the direction of this effect was accentuated by quaternization. Experience with certain of the synthetic paralyzing materials strongly fortifies the assumption that attenuation of the onium charges in poly quaternary ammonium compounds results in the progressive conversion of an intense depolarizing agent to one that prevents depolarization. For example, Bovet et al.[67] prepared a series of choline ethers of poly phenols and found that compounds like bis (beta triethylaminoethoxy) 1,2 benzene triiodide and tris (beta triethylaminoethoxy) 1,2,3 benzene (flaxedil®) (Fig. 11) were active curariform agents whose effects could be abolished with neostigmine. Two chemical considerations are prominent in considering the structural basis for the curariform activity of these compounds. Firstly, the ethonium groupings would be expected to have a lower effective charge than a methonium group as described previously for the simple mono onium ions. Secondly, as outlined in a preceding section, the proximity of the reacting groups would impair ionic reactivity. Accordingly, flaxedil is not a depolarizing substance but rather a curare-like agent. It is possible to demonstrate in another way the transition between the two types and the importance of proximity of reacting groups in the poly quaternary ammonium compounds. In Figure 12 are illustrated the formulae of certain methonium analogues of the flaxedil type. On the basis of what has been said, it might be predicted that the methonium groups, rather than ethonium groups, would restore the effectiveness of the onium charge and thereby produce neuromuscular block through excessive depolarization. In compound A of Figure 12, the two methonium groups are separated by virtue of their meta orientation on the benzene ring and, accordingly, the paralysis produced by this agent is not antagonized by neostigmine.[68] In compound B of Figure 12, the insertion of a third methonium group in the 2 position introduces the proximity effect and impairs the ionic reactivity of the compound. In this instance, the paralysis produced by the compound is curariform and is counteracted by neostigmine or tensilon.[69]

Although these considerations may explain the absence of a significant depolarizing action

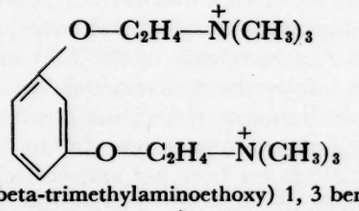


Bis (beta-triethylaminoethoxy) 1, 2 benzene

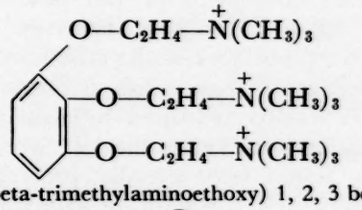


Tris (beta-triethylaminoethoxy) 1, 2, 3 benzene
FLAXEDIL

FIG. 11.



Bis (beta-trimethylaminoethoxy) 1, 3 benzene
A



Tris (beta-trimethylaminoethoxy) 1, 2, 3 benzene
B

FIG. 12.

for d-tubocurarine, they still do not clarify the action of curare to prevent depolarization. Pfeiffer[58] has suggested that ACh blocking agents like atropine gain attachment to the cell surface through their reactive groupings and prevent the smaller molecule, like ACh, from reaching the critical site. The large molecular structure of atropine was conceived as providing either steric hindrance to the accession of ACh or electrostatically inactivating adjacent receptor sites. Similar speculations may be applied to the blocking of the motor end plate by curare, but the present status of our knowledge does not furnish an answer to the question.

It would indeed be unfortunate if the impression were made that agents that disrupt neuromuscular transmission act exclusively by either one mechanism or the other. In the flaxedil® series it has been observed that the successive replacement of the ethonium radicals by methonium groups resulted in compounds that superficially exhibited a curariform activity, but on closer examination, it was found that this action was actually preceded by a period in which transient depolarization appeared.[69] Even the paralyzing action of curare itself is not pure; it has been noted that curare is capable of producing some slight degree of excitation[70,71] prior to the prevention of depolarization. Most recently, it has been demonstrated by Zaimis that the paralyzing action of C 10 is impure. It was suggested that this compound, depending on the species and on the type of muscle involved, may produce a form of paralysis that closely resembles that established by d-tubocurarine.[72] These experiments with C 10 remain to be confirmed, but it is clear that one cannot look upon either type of blocking action as exclusive of the other. Particularly with the introduction of many new synthetic compounds it would be unwise not to recognize the possibility of gradation of action from one type to another.

ANTI-ChE ACTION

Prior to considering those particular substances that have anti-ChE activity, it is preferable to discuss the effects of ChE inactivation at the n.m.j. Perhaps the most widely known effect of an anti-ChE drug, like physostigmine, on the neuromuscular apparatus is the development of fasciculatory twitchings shortly following its administration to the experimental animal. If it is assumed that the principal action of the drug is to inactivate the ChE, this observation suggests that the observed effect is due to the accumulation of endogenously formed ACh. Obviously, the greater the neuromuscular activity the more rapid will be the accumulation of ACh. However, the intra-arterial injection of an anti-ChE agent also results in the appearance and development of fasciculations in the unstimulated muscle. The fasciculations continue to grow in intensity and the conclusion that ACh is released continuously is consonant. Direct proof of continuous subliminal activity at the n.m.j. has been furnished recently by Fatt and Katz,[73] who showed that the resting muscle exhibits at the end plate region miniature potentials that are localized and non-propagated. The inhibition of ChE increased the magnitude of these small local potentials and curare suppressed them. It was concluded that there is a steady release of ACh in subliminal concentration by the motor nerve.

Probably the earliest and perhaps one of the most significant observations on an anti-ChE drug was made by Langley and Kato[74] shortly after the turn of the century when they observed that physostigmine did not increase the fibrillatory activity of chronically denervated muscle. Since that time there has been adequate demonstration of the fact that drugs that exhibit only anti-ChE activity are without effect on the chronically denervated mammalian muscle.[39] From this it is evident that the intercession of endogenous or exogenous ACh is requisite for the development of effects after inactivation of ChE. In chronically denervated muscle, ChE remains localized in the region of the end plate and is susceptible to inactivation as in the normal muscle.[75] In consequence, anti-cholinesterases are known to increase the sensitivity of chronically denervated muscle to exogenous ACh but that they are without an overt effect connotes the absence of neurohumoral activity in this structure.

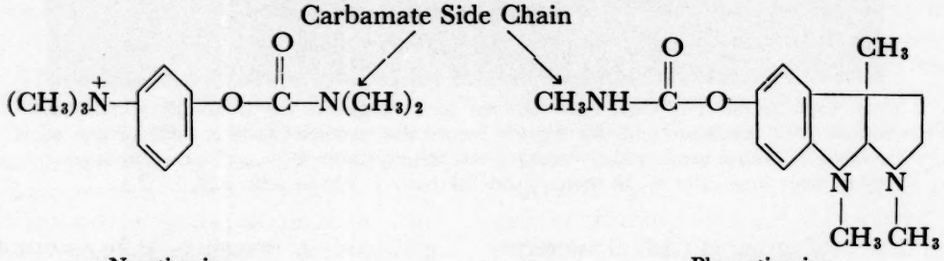
The characteristic effect of ChE inhibition to prolong the action of ACh may be detected readily from the observation that the close arterial injection of ACh into a muscle responding to single maximal nerve shocks results in, at best, the potentiation of only a single twitch, but if a small dose of an anti-ChE agent is first given, the subsequent administration of ACh results in an enhancement of the tension response.[3,6] Congruent with the remarkable similarity between the effects of ACh and nerve

FIG. 13. The effect of ChE inhibition on the response of the indirectly stimulated muscle. The myogram and electrogram record the response of the cat tibialis ant. to a single maximal nerve volley twenty-seven minutes after 0.72 μ of intravenous physostigmine; time interval 10 msec. (After BROWN. *J. Physiol.*, 89: 220, 1937.)

stimulation the inactivation of ChE alone serves to increase the effects of motor nerve activity. For example, if a muscle is responding to single maximal motor nerve shocks, the administration of an anti-ChE agent produces an increase in the tension developed from each contractile response. Obviously, this can only mean that the single twitch has been converted into some form of incomplete tetanus. The veracity of this is borne out by electrical recording and is illustrated in Figure 13. In this experiment when a suitable dose of physostigmine was given intravenously, the maximum potentiation of the response to indirect stimulation was reached within five or ten minutes. This action was lasting, for it could be detected as long as 140 minutes after the drug administration. With the electrical recording (Fig. 13) it was possible to show that physostigmine converted the response from a single nerve shock to a propagated repetitive discharge approaching momentarily a frequency as high as 600/sec. The discharge was at first synchronous, but this phase usually did not continue for more than 30 to 40 msec., after which extreme asynchrony developed. As the effect of physostigmine deteriorated, the discharge frequency developed by each nerve impulse fell progressively. The intensity of this tetanic response depends on the anti-ChE potency of the particular drug used. The duration of the effect depends on the rapidity with which the enzymatic activity of the junction is restored; this in turn reflects the extent of reversibility of the inhibitor-ChE combination. It must be recalled at this point that the paralyzing action of quaternary ammonium compounds represents an extension of their excitatory effects. In this regard the inactivation of ChE, if of sufficient magnitude, will lead to excessive ACh accumulation and depression of neuromuscular transmission will result. As a corollary, in the presence of ChE inactivation, superposition of a quaternary ammonium substance, having excitatory properties, may quickly lead to a blockade of transmission. Thus the administration of C 10 following ChE inactivation will produce a more severe paralysis that may also be unduly prolonged.[46]

From the pharmacologic standpoint, a significant detail of drug action relates to the time course over which that action is developed. To analyze this for drugs acting at the n.m.j., it is best to utilize the close arterial route to minimize temporal dispersion of drug action. In an experiment performed by Bacq and Brown[33] it was found that an optimal dose of physostigmine given by this route resulted in a gradual increase of the muscle response that reached its maximum in about two minutes. Clearly, the progressive nature of this action is contingent on the accumulation of optimal concentrations of ACh at the several motor end plates. With the introduction of the alkyl fluorophosphates during World War II, a new principle was made available for application in studies on synaptic transmission. One of the substances, diisopropylfluorophosphate (DFP), received extensive study. This compound was found to produce an irreversible inactivation of the numerous cholinesterases in blood and tissues.[76] For recovery it was necessary for the animal to synthesize new enzyme protein at each of the specific sites affected. This contrasted sharply with the reversible inhibition of ChE produced by physostigmine, wherein the inhibited enzyme was gradually released from combination to function again as the drug was eliminated. However, regardless of the mode of inactivation

of ChE, the qualitative effects on neuromuscular function are the same. Accordingly, the effects of DFP are more prolonged than those of physostigmine, and it has been found that the chronic depletion of neuromuscular ChE with DFP results in the development of easy fatigability and weakness in the animal poisoned.[77] When DFP is administered by the close intra-arterial route to a muscle responding to single maximal motor nerve shocks, an increase in the tension of the response develops over a gradual course like that described for physostigmine.[78] The attainment of the full effect requires the intermediation and summation of neural activity. Other factors will also influence the speed of development of the effects of an anti-ChE drug. Chief among these is the rate at which the drug combines with and inactivates the junctional ChE. This will vary for different drugs. Thus the reaction between ChE and physostigmine or an alkyl phosphate, like tetraethylpyrophosphate (TEPP), occurs most rapidly; the reaction between DFP and ChE is relatively slow.[79] Despite the rapid inactivation of ChE by TEPP, the optimal potentiation of the contractile response is achieved through a graded effect, although the development of the entire effect occurs more rapidly than with DFP or physostigmine.[80] Finally, the potency of the anti-ChE activity must be considered. Recently a bis-quaternary ammonium ion having an exceedingly high anti-ChE activity* when injected into the arterial supply of the cat neuromuscular preparation produced a rapid enhancement of the response to single maximal nerve shocks, but once again the optimum was reached in progressive fashion.[81] Other factors such as the ratio of water to oil solubility will determine in part the anti-ChE effect at the n.m.j.[83] Nachmansohn has pointed out that those agents, such as quaternary ammonium



Neostigmine
(Quaternary N^+)

Physostigmine
(Tertiary N)

FIG. 14.

ions, that have a high aqueous solubility may be expected to act at the n.m.j., while those that are primarily lipoid soluble will be inactive.[84] DFP, because of its high lipoid solubility, must be given in relatively large dosage to achieve an effect at the n.m.j.

After Stedman[85–87] had made it apparent that the anti-ChE activity of physostigmine was traceable to the carbamate grouping, the preparation of synthetic carbamate derivatives provided several compounds for study. In one such investigation, Aeschlimann and Reinert[88] found the dimethyl carbamic acid ester of 3-OH-phenyltrimethylammonium bromide to have strong anti-ChE activity accompanied by typical physostigmine-like effects. This compound, marketed under the name of prostigmine® and officially called neostigmine, also possessed a high degree of anti-curare activity. For this reason, it was chosen for clinical trial in myasthenia gravis, a disease that simulates, unusually closely, the state of partial curarization in the experimental animal.[89] The efficacy of neostigmine in this condition proved remarkable. In fact, it was described by Walker and others as superior to physostigmine in effecting a response in the afflicted individual.[90,91] This observation parallels the later finding that neostigmine is also the more efficacious anti-curare agent.[63,64] If the inhibition of ChE were the sole factor in the achievement of these pharmacologic effects, neostigmine and physostigmine should prove approximately equal in their activities, since their anti-ChE potencies

* The compound, bis (3-phenoxy trimethylammonium iodide) 5′dimethylaminocarbamyl-1,3 propane in a molar conc. of 6×10^{-11} *in vitro*, inhibits the activity of a specific ChE by 50 per cent.[81] The equivalent conc. of physostigmine required is 8×10^{-7} M.[82]

are not considerably different.[79,82] The discrepancy in their pharmacologic actions relates to their differing chemical structures. A comparison of their formulae (Fig. 14) reveals that neostigmine is a quaternary ammonium base, having the trimethylated nitrogen moiety characteristic of ACh, whereas physostigmine is a tertiary amine. The inactivity of the tertiary amines on the n.m.j. has already been emphasized and attention has been directed to the high affinity of the trimethylated quaternary ammonium bases for the n.m.j. Therefore neostigmine, because of its cationic head, should make ready union with the receptor substance of the n.m.j. as well as with the ChE. In addition neostigmine, like ACh, has a carbonyl grouping as part of its ester structure, and the distance of this grouping from the onium center is similar to that distance in ACh.[58] It is not unreasonable to suspect that neostigmine will complete attachment to the receptor through its carbonyl grouping in a manner similar to that proposed for ACh. Following such a reaction of neostigmine with ChE or receptor, hydrolytic cleavage of the ester link would be unlikely because of the stability of the carbamate link as contrasted with the acetyl ester. In this way it may be seen that neostigmine has the potential for a twofold action. Through its cationic head it may directly initiate excitation at the motor end plate as well as to achieve union with the enzyme if these be different. Furthermore, the carbonyl grouping will serve to effect a firm union with the ChE and possibly complete a reaction with the receptor. Thus an initial excitatory action would be fortified by the cumulation of ACh resulting from the inhibition of esterasic activity. That neostigmine possesses such a capacity for direct excitatory action was demonstrated through recognition of the fact that chronically denervated mammalian muscle, a tissue unresponsive to inhibition of its ChE by DFP or physostigmine, responds to the application of neostigmine with an effect that is qualitatively identical to that elicited by ACh and related quaternary ammonium bases.[92] In addition, when neostigmine is injected by the close arterial route in a muscle responding to maximal nerve stimuli, exceptionally fast achievement of the optimal increase in twitch tension may be seen.[39] This action of neostigmine is dissimilar to the less striking effect of other anti-ChE drugs in this circumstance, and it likely reflects the dramatically rapid action of neostigmine in the myasthenic patient. The unusual effect of neostigmine at the n.m.j. must attribute in part to a direct action on the end plate.

To analyze the direct component of neostigmine action, it was deemed desirable to isolate the cationic head of the ester and simultaneously eliminate the ChE inhibiting action of the carbamate fraction. A dissection of the molecule was made by first replacing the dimethyl carbamate moiety with the simpler acetyl esterification; this was intended to abolish the anti-CHE activity and to increase the resemblance to ACh.[39] The resulting compound fell somewhat short of expectations since there remained some residual anti-ChE activity, but it was of a low order of potency and of a strict competitive nature. Wilson[93] has demonstrated the fact that quaternary ammonium ions will react with the anionic site on the specific ChE in the same manner as ACh. In this way, competitive inhibition of the normal substrate occurs. Despite this weak competitive inhibitory effect on ChE, the 3-acetylphenyl trimethylammonium ion exhibited a potent and highly restrictive action on the mammalian n.m.j. The major manifestations of this action included the elicitation of a contractile response on close arterial injection, the potentiation of the response of the indirectly stimulated muscle, the production of contraction in chronically denervated muscle and an efficient anti-curare action. Subsequent experiments soon made apparent the fact that all of these effects could be achieved equally well with the simple unesterified base, 3-OH phenyltrimethylammonium ion.[28] Especially unlike the anti-cholinesterases, the potentiation of the muscle response to indirect stimulation was characterized by an immediate attainment of the optimal tension from which the effect decayed gradually. Also different from the ChE inactivators was the comparatively short-lived nature of the response to these ions (2–3 min.). The direct action of both ions was also evidenced by the immediately maximal nature of their anti-curare action. The practical use of the 3-OH phenyltrimethylammonium ion type has established it as the anti-curare agent of choice because of the negligible side effects associated with its administration as well as its brevity and specificity of action.[94] As one might expect, an agent like 3-OH phenyltrimethylammonium ion is highly effective in myasthenia gravis, but its transitory action makes it useful only as an experimental

tool.[95] On the other hand, its efficient anticurare action is in part attributable to an associated displacement and elimination of curare. The 3-OH phenyltrimethylammonium ion, like the phenyltrimethylammonium and tetramethylammonium ions, must be classed as a direct acting agent. In turn, the complex nature of the neostigmine action is apparent.

Specificity of therapy is usually a desirable feature and those actions that result from the indiscriminate inhibition of ChE, at neuroeffector sites other than the desired one, are classified as side actions. To achieve the necessary inhibition of ChE at the n.m.j. only, a water soluble agent having a nearly unique specificity for this enzyme is requisite. At present there is no evidence to indicate that the specific ChE of the n.m.j. is singularly different from specific ChE at other neuroeffector sites in the same species. For example, stimulation of the gastrointestinal tract and secretory glands have been objections to the use of neostigmine and physostigmine in the management of myasthenia gravis. With TEPP beneficial effects in the treatment of myasthenia gravis can be achieved.[83] However, the margin between the therapeutic effect and toxic effects, especially actions on the central nervous system, is a small one. Therefore, the use of this agent clinically requires most careful observation. DFP has proved particularly disappointing in the management of myasthenia gravis, because the doses needed to achieve the critical inactivation of ChE at the n.m.j. produce unwanted effects on the gastrointestinal tract, central nervous system, glands of secretion, etc.[96] Another alkyl phosphate, octamethylpyrophosphoramide (OMPA), has been found to be a potent anti-ChE *in vivo*.[97] *In vitro* this substance has little ChE inhibitory action, but given to the intact animal, it undergoes conversion in the liver to a potent anti-ChE substance. The distinguishing feature of this material is that it does not penetrate the blood-brain barrier and the brain ChE remains at a normal level even with lethal amounts. However, the peripheral ChE of the gastrointestinal tract, blood, secretory glands and n.m.j. are affected to a nearly equal degree. Therefore, there is no reason to believe that this compound will offer any advantage over other anti-ChE substances. The problem is not one of potency, and the search for more potent anti-ChE drugs can have little clinical significance. If the management of myasthenia gravis is to be achieved through the inhibition of ChE, the quest must aim at specificity, admittedly a different goal.

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Conference on Therapy

Some Therapeutic Applications of Vasodilating Agents

THESE are stenographic reports, which have been edited, of conferences by the members of the Departments of Pharmacology and of Medicine of Cornell University Medical College and the New York Hospital, with collaboration of other departments and institutions. The questions and discussions involve participation by members of the staff of the college and hospital, students and visitors. A selected group of these conferences is published in an annual volume, Cornell Conferences on Therapy, by the Macmillan Company.

DR. GEORGE READER: We have had several requests for a discussion of the subject of the therapeutic application of vasodilating agents. This material will receive an airing in the conference today. Dr. William Foley has given much thought to this subject and he will open the discussion. It will be continued by Dr. Burke and members of the Department of Pharmacology.

DR. WILLIAM FOLEY: I shall direct my remarks chiefly to the problem of vasoconstriction and vasodilatation in the limbs. Their surface constitutes about two-thirds of that of the whole body, and in the current custom of dress they are the most exposed parts of the body. Since vasoconstriction and dilatation are a means of regulating body temperature, these processes in the limbs play a dominant role in regulating heat loss. Changes in the peripheral vasomotor tone occur under a variety of physiologic stimuli. There is the familiar blush which occurs with embarrassment. This results from a psychologic stimulus, an action on the central mechanism for vasodilatation, giving rise to a generalized dilator result most noticeable in the face, but also involving redness of the hands. Warming the blood causes a generalized relaxation of the blood vessels by an action on the central vasodilator mechanisms. It takes place when one passes from the outside cold into a warm room in the winter or when one soaks a limb in warm water. This is in fact one of our most useful measures for producing vasodilatation. When a generalized vasodilator action is necessary, one may instruct the patient to sit in a tub of warm water at a temperature of 100°F., a temperature which is a little higher than that of the body, and do so for about a half hour at a time. This gentle warmth usually produces a maximum degree of vasodilatation. A similar result can be obtained by applying a hot water bottle or heating pad at a point proximal to the area that needs the increased blood flow. This position of the locally applied heat results not only in a reflex vasodilatation in the particular limb but also generalized vasodilatation.

Among chemical agents which produce vasodilatation, there are histamine and acetylcholine as the two compounds formed in the body. Histamine produces a vasodilatation of arteries and minute vessels. It produces a vivid flushing of the skin, rise of the skin temperature, headache and may cause a marked fall of the blood pressure. These changes result when it is injected intravenously, and when used in this manner, the vasodilatation is fleeting and not of any particular therapeutic value. However, there is a manner in which histamine can be used with considerable value for dilating the vessels of a leg. The technic was introduced several years ago by Mufson at one of our neighboring medical centers. He described the use of histamine diluted in 1,000 cc. of physiologic salt solution and infused through a needle in the femoral artery so slowly that it fails to get into the general circulation in any sufficient concentration to cause trouble while at the same time remaining in high enough concentration in the limb to give rise to effective vascular dilatation. The technic is troublesome and it takes time to master it. For this reason the method is not very extensively used, but we have employed it from time to time and it is a distinctly valuable form of treatment for improving the circulation in a limb.

The other naturally occurring compound, acetylcholine, has not proved particularly useful as a vasodilator. It is effective enough in dilating vessels but its action is much too fleeting. There have been many attempts to synthesize acetylcholine derivatives with the object of securing compounds which might slowly liberate acetylcholine in the body. These have also not proved particularly successful. One of the last of these to come to our attention is a manganese salt of acetylcholine, a French product called protenzyl.® There are large numbers of papers in the French literature lauding its benefits in hypertension and various vasospastic states. We tested it in normals and in various vascular disorders and were unable to demonstrate effects in either.

Fever is a very potent cause of vasodilatation. It is the mechanism in disease which helps to provide for the dissipation of heat. Fever artificially induced is used for therapeutic purposes. Various types of protein have been injected in this connection, sterile milk and others, but typhoid vaccine is generally the material of choice and we have found it easier to regulate the amount of fever with this material. We usually start with 5 million organisms injected intravenously. We aim to produce only a small rise of about 1° to 1.5°. Larger doses will, of course, produce greater rises of the temperature but they are apt to be preceded by a chill and the chill produces the unfavorable effect of a vasoconstriction. The dose may be repeated every second or third day depending on the patient's condition; and since patients tend to develop an immunity to typhoid vaccine, the succeeding doses have to be increased. We have found the plan of increasing the dose by about 3 million at each successive injection a generally practical one. This method of typhoid vaccine injection produces very good vasodilatation. It has proved especially useful in the treatment of thromboangiitis which in the acute stages is attended by marked vasospasm causing considerable pain.

Mention may be made of the surgical means for producing localized vasodilatation. It has long been known that the surgical removal of the inferior cervical ganglion or its destruction by disease produces vasodilatation in the face and upper limb, also Horner's syndrome. The same results in the legs during spinal anesthesia, and in the foot when the lower lumbar ganglia are removed. The operations of lumbar or dorsal sympathectomy have been devised for this purpose. The part becomes red, warm and dry.

To come back to the chemical vasodilator substances, I should like to refer especially to the nitrites as the best representatives of dilator materials foreign to the body. Our attention was called to the possible utility of the nitrites in cervical vascular disease by an experience with a patient, a gentleman of about sixty, who took nitroglycerin for the relief of the pain of angina pectoris. He also had Raynaud's phenomenon in his fingers, with blanching. It was secondary to arteriosclerosis of the digital arteries. He noted that a tablet under the tongue not only relieved the cardiac pain but produced flushing of his fingers. It was this experience that induced us to make a further study of nitroglycerin in peripheral vascular disease. We have analyzed our experience with ninety-six subjects observed under controlled conditions, nineteen of them with normal vasomotor tone and twenty-nine with increased vasomotor tone. There were cases of Raynaud's disease, acrocyanosis, livedo reticularis, thromboangiitis obliterans, arteriosclerosis with and without occlusion. Observations were made on the vasomotor tone in the hands and feet, the strength of all the peripheral pulses, oscillometric readings on the feet, the legs, the hands and arms. In many of these cases changes in skin temperature and arterial pulsations were tested in a constant temperature room. The results were very interesting. Within a few minutes after a tablet of nitroglycerin under the tongue, pulsations often appeared in limb vessels in which they were previously imperceptible, in others marked increase in the size of the pulse was detected in large vessels such as the dorsal pedal artery. The effects were more pronounced in subjects with previously increased vasomotor tone than in those with normal tone. Oscillometric readings frequently increased. These effects were noteworthy in patients in whom increased vasomotor tone produced cold hands and feet in the absence of manifest disease, the kind of abnormality which in more extreme degrees causes intense blanching or cyanosis as in Raynaud's disease or acrocyanosis. The blood pressure changed very little after the nitroglycerin when the patient was in the horizontal position. The effect on the pulse rate was variable; sometimes it rose and sometimes it fell. Of course, in those cases in which there was organic occlusion of the vessels no change in

pulsation resulted. It is also noteworthy that these changes took place without any appreciable change in the skin temperature. We interpreted the results to mean that nitroglycerin is a strong dilator of large arteries, that it increases the blood flow to the part, and that it is valuable both as an aid in diagnosis of spasm of vessels in the limbs and for purposes of treatment.

There are other vasodilator drugs which deserve mention. Alcohol should head any general list. If it is taken in accordance with the advice of Aristotle, in moderation, it is of great benefit in warming not only the personality but the skin. Nicotinic acid is an effective dilator but its effects are too fleeting. We have not found it particularly valuable.

In the past few years we have tested a large variety of the newer sympatholytic and adrenolytic agents for dilating the limb vessels in peripheral vascular disorders. Generally speaking, they produce fairly pronounced dilatation but their utility is limited by the brevity of the effect and the disturbing systemic symptoms. This is true of tetraethyl ammonium chloride which has received fairly extensive trial. It is effective only by injection. Priscoline,® the trade name for a derivative of imidazoline, is active orally, producing the vasodilatation partly by blocking at the ganglia and partly by histamine-like direct action on the vessels, and is of especial benefit by intra-arterial injection. The sympatholytic effects of the hydrogenated alkaloids of ergot, marketed under the name of hydergine,® have come in for a good deal of attention in the past few years. In normal subjects we have not been able to discover any peripheral vascular action of this material and we have not been able to confirm the reports of others to the effect that it possesses central vasodepressant action.

One of the most interesting compounds we have encountered in this group is the product 688-A* under the trade name of dibenzaline.® In one of the first cases in which we used it in the recommended dose in an intravenous infusion over a period of an hour it produced practically complete paralysis of the sympathetic control of the vascular bed for a period of about four days. The patient was not able to sit up; when he did the blood pressure fell to zero. The skin of the hands and feet became strikingly warm, red, and dry. The workers at the Goldwater Memorial Hospital have been using this drug in fairly large doses for the treatment of hypertension. It may turn out to be a valuable addition to the list of agents which are now being studied for the generalized dilatation of blood vessels.

* This is a product of Smith, Kline & French.

DR. READER: Dr. Burke, would you be willing to take a few minutes to discuss this subject?

DR. GRAFTON BURKE: I should like to call attention to some of the uncertainties concerning so-called vasodilator drugs. There is much disagreement both among pharmacologists and clinicians as to what the vasodilator drugs accomplish in terms of blood flow. Dr. Foley indicated that nicotinic acid is not especially useful as a dilator agent although it does cause vasodilatation. We are all familiar with the flushing of the face which occurs when it is used in the treatment of nicotinic acid deficiency. There is the evidence, however, that even though it reddens and warms up the skin, the vasodilatation applies only to the skin capillaries, vasoconstriction resulting in other parts of the limb with a total decrease in the blood flow. Papaverine® is another drug in point. It is widely used and may possibly have some value in obliterative arterial disease but the evidence for its value is extremely shaky. The group in Boston gave very large doses of papaverine without appreciable effect. Similar doubt concerning utility applies to the synthetic analogue of papaverine supplied under the trade name of papaveril,® concerning which there are now several reports in the journals. The evidence indicates that it dilates the capillaries of the skin but by the measurement of the uptake of radioactive sodium from the gluteal muscle it appears to exert no appreciable effect on the blood flow through the limb. Tetraethyl ammonium and hexamethonium (methonium®) produce a good deal of vasodilatation but too many unpleasant side effects. I recently spoke to the medical director of one of the companies which supplies hexamethonium and I learned of the possibility that the material may be withdrawn from the market because of the unexpected incidence of hazardous side effects.

I should like to enlarge on Dr. Foley's remarks concerning histamine. Dr. Sorenson and a number of our own group found that the uptake of radioactive sodium injected into the calf muscles is increased by the intravenous infusion of histamine, a fact which may be interpreted as increased blood flow through the muscles.

As Dr. Foley indicated, the proper technic of the infusion is a decisive matter. The method we use is to put 2.75 mg. into 500 cc. of physiologic salt solution and inject it slowly intra-arterially, at the rate of 60 drops a minute, the speed being regulated by the pressure of the cuff of a sphygmomanometer. We had one patient who developed profound shock when the injection was too fast, but with strict attention to the matter of keeping the injection very slow such reactions can be prevented.

There is one other point I think is worth while making and that is that regardless of how potent the vasodilator agent that is used, factors exist in the vasospastic condition which may greatly limit its usefulness. There is the well known fact about sympathectomy in Raynaud's disease that even after a very successful operation the phenomenon tends to recur.

DR. HARRY GOLD: How does it happen that the dose is so precise, 2.75 mg.? Is it that because the ampule provided on the market happens to contain 2.75 mg.?

DR. BURKE: Yes, that is the answer. Just a word about the clinical management of the acute arterial occlusion due to embolus or thrombosis. If we decide that an embolectomy is not to be performed at once, a regimen of anticoagulants and strong vasodilators is started. As for the dilators, we employ priscoline or histamine intra-arterially into the vessel of the limb involved. We also make use of the oscillating bed and apply "reflex heat" in the manner already mentioned by Dr. Foley. We never apply heat directly to the part of the extremity involved in the occlusion. I should also mention that we employ large doses of whiskey. There are problems in differential diagnosis. One cannot always be certain that the artery has been occluded and in that case sympathetic or spinal block help to differentiate between a vasospastic and an embolic state. It is well to do this if an embolectomy is being considered. There have been persons in whom the operation for embolectomy was performed only to discover that it was a spasm of the femoral vein in sufficient degree to obliterate the arterial pulse. Sympathetic or spinal block helps to rule out these cases. As for sympathectomy, we do not like to do this operation for arteriosclerosis obliterans. It is best suited to patients with Buerger's disease after a trial period of four to six months in which the patient has gone without smoking.

DR. READER: Thank you, Dr. Burke. Are there any questions?

DR. SOLOMON GARB: I believe it is well known that a reciprocal relationship exists between the state of the vascular bed of the skin and that of the muscles, and that when something is done to dilate the vessels of the skin it is likely to give rise to a contraction of the vessels of the muscles. Is it not a fact that the measurements in the studies on vasodilator agents usually relate to the skin and might therefore give us an erroneous impression of the blood flow through the muscles which would appear to be the more important consideration in vascular disorders of the limbs?

DR. BURKE: What you say is in the main true, Dr. Garb. However, some studies of the vascular bed in the muscles have also been made and there is the technic which has been applied in more recent investigations in which radioactive sodium is injected into the leg muscles, the uptake from the muscle being a fairly satisfactory index of vasodilatation in the muscles. I should also mention that the condition of the skin cannot be altogether ignored, for it is in the skin that the gangrenous necrotic ulcers first appear in obliterative arterial disease.

DR. GARB: There still remains, however, the case with intermittent claudication in which I take it the circulatory difficulty relates to the muscles. How about the group of vasodilator drugs in regard to these?

DR. BURKE: The evidence is not at all conclusive. I for one am not at all enthusiastic about the vasodilators.

DR. READER: Dr. Ferguson, might we have some comments from you on this subject?

DR. FRANK C. FERGUSON, JR.: Dr. Burke's lukewarm enthusiasm for the use of vasodilating agents to improve the circulation in the skeletal muscles in peripheral vascular disorders encourages me to add to the strength of the case against them. Dr. Foley mentioned the fact that one of the primary biological functions of vasodilatation in the skin is to enable the body to lose heat. From the theoretical standpoint it would seem to me a strange mechanism if at the same time that vasodilatation occurs in the skin, vasodilatation would also occur in the muscles which would have the effect of drawing blood away from the skin and thereby thwart the possible attempt to lose heat. In actual fact, as far as I am able to judge from the literature, the biological purpose of vasodilatation in the skin

is not easily thwarted. The experiments on man, and also those on animals, seem to show in the main at least that when the skin vessels are dilated by whatever agent is used the muscle vessels constrict. To be sure, the evidence is not altogether consistent and many of the reports in the literature are indecisive. There is the action of the sympathetic nervous system which when excited causes vasoconstriction in the skin and vasodilatation in the muscles. It is conventional to speak of sympathectomy as leading to increased blood flow in the limb with the implication that there is increased blood flow through the muscles of the limb. It is true that after this operation the size of the pulse increases, the skin becomes flushed and warm and the volume of the limb increases, but there is much evidence to suggest that this is associated with more blood and possibly greater blood flow in the skin and subcutaneous tissues at the expense of the muscles where compensatory constriction occurs and flow is diminished. This reciprocal relationship between skin and muscles has been shown by muscle temperature measurements as well as by measurements of radioactive sodium uptake from muscle during the action of various vasodilating agents, such as papaverine, alcohol and some of the newer autonomic blocking agents. I can understand the possible utility of vasodilator agents for the control of the skin ulceration of Raynaud's disease to which Dr. Burke referred; but if the problem is one of saving a limb that might otherwise become gangrenous due to severe reduction of the blood supply to the deeper structures, I would question the utility of such treatment and even suggest the possibility that it may do harm.

Dr. Burke: I wonder whether you would wish to apply the notion of reciprocal vasodilatation in the skin and vasoconstriction in the muscle to the effects of intra-arterial injections of histamine or priscoline. We have employed these agents by intra-arterial injection in the treatment of a sudden arterial occlusion.

Dr. Ferguson: I can see the possibility that a foreign dilator agent with an indiscriminate action on smooth muscle of blood vessels might cause dilatation in both the skin and the muscles simultaneously, although I have the firm conviction that the body which retains a semblance of its homeostatic mechanisms would have some way of getting around that and preventing it. If you say that the intra-arterial injection of histamine or priscoline is beneficial in a person with a sudden arterial occlusion, we shall have to accept that. I should like to register the fact, however, that there is some contrary experience on vasodilatation in the muscles after intra-arterial injection of papaverine. In these experiments on man the result was vasoconstriction in the muscles. There is also some evidence that with the intra-arterial injections the drug does not remain confined to the limb injected, and that vasodilator effects are also obtained in the opposite limb. I am not sure of the situation with intra-arterial histamine, but then papaverine has an action similar to histamine, directly on smooth muscle without relation to innervation.

Dr. Foley mentioned that there exists a difference between the response of vasospastic and normal vessels, and that an agent may produce vasodilatation in spastic vessels in doses which are ineffectual in normal vessels. From examination of the literature, I have found indications that that point also is undecided.

Dr. Gold: Could we possibly get on the outside of this discussion for a moment and perhaps have a look at the problem empirically? Clearly, there is conflict in regard to the mechanisms of action and to attempt to deduce from theoretical considerations the answer to the question as to whether these agents will do patients some good is not likely to be a fruitful exercise. It does seem, therefore, that what we need is a direct answer to this question: Are these vasodilators of any value in persons who have peripheral vascular disease, and perhaps we should include hypertensive disease? I can see the need of distinguishing here between their possible value in some acute vascular situation, as an embolus or thrombosis, from their long-range value in chronic vascular disease with impaired circulation. Could we have some opinions, or evidence if there is any, concerning the course of patients treated with and without vasodilator agents?

Dr. McKeen Cattell: Since the pharmacologists are having a field day today, I might also add a question. I find it hard to perceive the logic in artificial fever as a means of improving blood supply in the muscles. Fever increases heat production and leads to vasodilatation in order to promote heat loss, but the increased heat production is associated with an increased metabolism which in turn requires an increased blood flow to the part. It would seem, therefore, that the benefits of increased blood flow

in the limb might be cancelled out by the increased demands made by the elevated metabolism. Under these circumstances the limb as a whole would not be any better off even if the blood flow is increased.

DR. READER: Dr. Foley, how would you handle these questions?

DR. FOLEY: I can tell you what seems to be true in the case of nitroglycerine, and there is some indication that it is also true about some of the other dilator agents. There is proof that nitroglycerin increases the cardiac output and that it does so in an individual in whom there may be no fall of the blood pressure. Whenever the combination of unaltered blood pressure and increased cardiac output exists, there must be increased blood flow; there is no other possibility under these conditions.

DR. FERGUSON: I do not take issue with the fact that there may well be increased blood flow. The points I raised in my discussion relate to the question where the increased blood flows. Is it through the skin and subcutaneous tissues or through the muscles?

DR. FOLEY: I believe there is increased flow through the muscles because, as I have already indicated, in our experiments with nitroglycerin the skin temperature remained unchanged, which means that the increased blood flow must take place through the muscles.

As to the point which Dr. Gold raised regarding the value of these drugs, I believe they are of great value. If an artery is partially occluded, or totally occluded, as many of them are by spasm, and the spasm is relieved, it is difficult to imagine that the patient will not be better off. The benefit in the case of the white finger of Raynaud's phenomenon is very easy to demonstrate.

DR. GOLD: I wonder whether Dr. Foley would be willing to extend his remark on relieving the blanching of the finger in Raynaud's phenomenon to the question of controlling the necrotizing lesions of the skin in Raynaud's disease, those situations in which the patient goes on losing tips of his fingers in the course of years. Can you put an end to that process by the prolonged use of vasodilator agents?

DR. FOLEY: I wish I had known the discussion would take this turn. I would have brought along with me some of the colored pictures which show conditions before and after treatment.

DR. GOLD: Tell us about them without the color.

DR. FOLEY: Perhaps it will suffice to mention again the fact that artificial fever is very effective in controlling the clinical course of thromboangiitis obliterans. The pathologic features of this disease are well known; they include changes in the skin as well as in the muscles. Vasospasm is an outstanding element in this disease.

As to Dr. Cattell's question concerning the mode of action of artificial fever, do you not agree that there is increased cardiac output in fever?

DR. CATTELL: Yes, I can agree to that.

DR. FOLEY: Would you agree that with this increased cardiac output there may be increased flow to the extremities?

DR. CATTELL: Yes, I could grant that point also.

DR. FOLEY: If the vessels are in such a degree of spasm that they allow only a small trickle of blood and the temperature of the extremities falls to that of the room, giving rise to trophic ulcers of the skin, does it not follow that vasodilatation would benefit the situation?

DR. CATTELL: Because of the increased metabolism in fever, the benefit of any increased blood flow might be erased on a theoretical basis. However, there can be no argument if you have found that such benefits actually occur.

DR. FOLEY: Yes, they do, the lesions tend to heal as a result of the treatment.

DR. GOLD: I should like to press my point a little further even though I think that Dr. Foley has already answered it. Let me put it this way: Would you regard it as beneficial treatment to carry patients with Raynaud's disease along on, say, a dose of nitroglycerin under the tongue every few hours during the day?

DR. FOLEY: Of course, other measures are also used at the same time; these patients have to give up smoking cigarettes, too.

DR. FERGUSON: I should again like to sharpen off the distinction between benefits that might occur in Raynaud's disease where the problem is one of skin vasoconstriction and vasodilatation from the benefits that might occur in other diseases in which the problem is one of the vessels in the muscles.

DR. FOLEY: Perhaps my position will be made clearer if I say that we see benefits from vasodilator agents only in cases in which vasospasm exists. There are the patients with intermittent claudication due to arteriosclerosis obliterans in whom the hands and feet are warm, vasomotor

tone normal, in whom vasodilator agents are of no particular benefit. It is otherwise, however, if vasospasm is superimposed on this condition.

DR. FERGUSON: But I would like to present the challenge on your own ground, namely, the case of reflex spasm in an arterial occlusion. Can you be sure that the vasodilatation which these dilating agents produce increases the flow in the muscles or only in the skin? I doubt the adequacy of the evidence on this point.

DR. BURKE: I think that Dr. Gold's point of viewing the utility of these measures by an examination of the clinical results is an important one. In this connection it might be mentioned that in the reports from numerous sources on fairly large groups of patients with obliterative arterial disease, regimens of treatment including cessation of smoking, priscoline or other vasodilator agents, whiskey, reflex heat and elevation of the head of the bed have shown a very high incidence of improvement, as high as 80 per cent of the cases. These patients show increased capacity for walking and decrease in the symptoms of intermittent claudication. The regimens are aimed primarily at alleviating the spasm. The result is that the need for amputations has become much less frequent. I believe that we have fewer amputations since we have employed these regimens systematically in this hospital. Our incidence of amputations has fallen lower than I believe in most hospitals in the country.

DR. GOLD: How important is the contribution of the vasodilator drugs to these fine results?

DR. BURKE: I cannot say which of the factors are most important, but the fact is that as a result of this regimen we lose fewer toes, fingers, hands and limbs.

DR. GOLD: There still remains the question, how important are the vasodilator agents?

DR. GARB: All these patients are instructed to discontinue smoking. Vasoconstriction is a well known effect of smoking. Might this be responsible for the satisfactory results with the various regimens which Dr. Burke mentioned?

DR. BURKE: As I have already stated, I do not know which of the factors are responsible or most important. The alcohol they are instructed to take probably plays a significant part.

DR. FERGUSON: I wonder about that. I believe that a person has to get half "potted" before any significant effect on the circulation takes place. I believe your patients receive fairly small doses. Experiments with alcohol indicate that it takes about 2 or 3 ounces to produce conspicuous changes in the blood flow.

DR. READER: Perhaps Dr. Simon would say a word about these matters. He has been measuring improvement in patients with peripheral vascular problems by their capacity to walk.

DR. EUGENE P. SIMON: I have been making observations on the effect of walking in these patients. The results are clear on the point that walking causes vasodilatation in the muscles in patients with arterial insufficiency. In these experiments we gave patients placebos and observed the time for the appearance of the pain of intermittent claudication during exercise on a motorized treadmill. It was necessary to consider not only the amount of walking but also the rate at which they walked. Many of these patients with peripheral vascular disease can walk fairly slowly, say, at the rate of about 70 feet per minute, until they are exhausted without developing pain but experience clear-cut symptoms of claudication after two or three minutes when walking at a speed of 140 feet a minute. With these factors controlled in our experiments, we found that exercise itself is perhaps one of the best, if not the best, form of treatment to increase the patient's capacity for exercise.

DR. GOLD: May we assume then that in your management of patients with intermittent claudication, you would recommend a system of walking exercises rather than a regimen of nitroglycerin?

DR. SIMON: I have had only limited experience with the vasodilator agents in these experiments. The results are indecisive; in some patients there seems to be some improvement while in others the reverse is sometimes encountered. I am not impressed with their value.

SUMMARY

DR. GOLD: This conference on the therapeutic application of vasodilator agents has been the scene of much spirited discussion between the pharmacologists and the clinicians. It revolved almost exclusively around the use of these agents in peripheral vascular disorders like Raynaud's disease, thromboangiitis obliterans and other forms of vascular conditions involving restricted blood flow to the skin and muscles of the limbs. The agents considered included not only some of the older and better known materials with a more or less indiscriminate vasodilator action on blood vessels without relation to their nerve

supply such as nitroglycerin, alcohol, papaverine, histamine, but also some of the autonomic blocking agents like priscoline, which because of their rather highly selective pattern of action present intriguing possibilities for therapy. Various shades of opinion regarding the value of these materials found expression, some of the clinical experts favoring their use strongly, others taking a more lukewarm position, others expressing doubt concerning their value. There was general agreement that the vasodilators are of no particular value in obliterative arterial disease unless there is superimposed spasm. The belief was fairly generally expressed that they are useful in such conditions as Raynaud's phenomenon or Raynaud's disease in which abnormal constriction of vessels in the skin is the chief problem. Attempts on the part of experts in the treatment of peripheral vascular diseases to make out a case for vasodilator agents against vasospastic conditions in the skeletal muscles encountered obstacles. The pharmacologists maintained that there is a biological reciprocal relationship between the state of the blood vessels in the skin and that in the skeletal muscles, vasodilatation in the skin being associated with vasoconstriction in the skeletal muscles. They questioned not only the theoretical basis for the use of vasodilator agents in intermittent claudication but also the clinical evidence on their utility in these conditions. Apparently excellent results are obtained these days with systematic regimens of treatment including vasodilator agents, so that the loss of limbs has been reduced to a minimum; but what part the dilating agents play in this remained without a decisive answer, one questioning whether the results might not be due to alcohol that these patients receive, another suggesting that cessation of smoking may be the essential component in the method of treatment. There was considerable discussion of the value of artificial fever in thromboangiitis obliterans and intra-arterial vasodilator agents for the acute situation of an arterial occlusion. Recent experiments on the use of nitroglycerin in vasospastic states were discussed. The conference closed with the interesting observations that graded exercise in the form of walking at specified speeds acts as an effective vasodilating measure in intermittent claudication and may well be more important in the long-range management of peripheral vascular problems than the medications in current use.

Erratum: In the Conference on Therapy entitled "Treatment of the Patient in Coma," published in our April 1953 issue, this sentence on page 475, "Occasionally thirty-six hours after treatment with glucose-insulin is started the patient may develop hypopotassemia with return of collapse." should have read "three to six hours."

Clinico-pathologic Conference

Differential Diagnosis of Chest Pain Terminating Fatally

STENOGRAPHIC reports, edited by Robert J. Glaser, M.D. and David E. Smith, M.D. of weekly clinico-pathologic conferences held in the Barnes Hospital, are published in each issue of the Journal. These conferences are participated in jointly by members of the Departments of Internal Medicine and Pathology of the Washington University School of Medicine and by Junior and Senior medical students.

THE patient, W. S. (No. 89293), was a white married salesman, seventy years of age, who was admitted to the Barnes Hospital for the first time on February 4, 1953, complaining of chest pain for thirty-six hours. The family history was of interest in that the patient's father and one brother had died of "heart trouble." The patient himself had enjoyed good health until nine years prior to admission when he began to note excessive sweating, nervousness, heat intolerance, palpitation and weight loss. A diagnosis of thyrotoxicosis was made and thyroidectomy was performed in another hospital. Following operation the patient was completely relieved of his symptoms. He took thyroid extract for an indeterminate time postoperatively but had not taken any in recent years. He was able to lead an active life in business, and had had no symptoms suggestive of thyroid insufficiency. For several years he had noticed intolerance to fatty foods, but he had never been jaundiced. In the year prior to admission he had had symptoms of mild prostatism.

The patient was apparently well until thirty-six hours before hospitalization when he noted the gradual onset of constricting retrosternal pain in the upper chest. The intensity of the pain gradually increased and was associated with a moderate amount of dyspnea. There was no radiation, however, and no sweating or weakness. About eighteen hours before entry the patient called his private physician who administered a hypodermic injection. Subsequently, although he noted residual "soreness" in the left upper chest, his other symptoms did not recur. He was advised to remain in bed until hospitalization could be arranged, but he continued to be up and around in the interval before admission. In retrospect the patient recalled that during the past two years he had slept more comfortably with his head on two pillows and had awakened occasionally with a sensation of breathlessness. The episodes, however, were short-lived and unaccompanied by chest pain or cough. The patient had no difficulty in falling asleep again promptly. He denied specifically previous chest pain, dyspnea or ankle edema, and gave no history of hypertension, diabetes or venereal disease.

At the time of admission the patient's temperature was 37.0°C., pulse 80, respirations 20 and blood pressure 140/100 mm. Hg. He was a well developed, well nourished male who did not appear to be in acute distress. He lay in bed with his head on two pillows and breathed normally. No cyanosis was detected. The sclerae were muddy and the pupils were small in size but they reacted well to light and accommodation. Examination of the fundi revealed moderate arteriolar narrowing and A-V nicking but no hemorrhages or exudates. The neck veins were not distended. The upper respiratory tract appeared normal. Percussion and auscultation of the chest was within normal limits. The heart was not enlarged to percussion, the left border of dullness being 6 cm. to the left of the midsternal line in the fifth intercostal space. The heart sounds were of good quality and the rhythm was regular. The aortic and pulmonic second sounds were equal in tensity; the first mitral sound was reduplicated. There were no significant murmurs. Abdominal examination was negative. Rectal examination was deferred. The arterial pulsations were easily palpable in both feet and there was no pedal edema or clubbing. The neurologic examination was normal.

The laboratory data were as follows: Blood count: red blood cells, 5,600,000 per cu. mm.;

hemoglobin, 17 gm.; white cell count, 18,000; differential count: 3 per cent band forms, 79 per cent neutrophils, 13 per cent lymphocytes, 5 per cent monocytes. Blood for cardiolipin test and urine and stool specimens were not obtained. Electrocardiogram: the changes were those of an acute posterolateral myocardial infarction with horizontal heart position. Prothrombin time: 100 per cent of normal.

The patient was placed on complete bed rest and anticoagulant therapy was begun. He was comfortable until the evening of the first hospital day when chest pain returned. The administration of dilaudid subcutaneously and of oxygen by nasal catheter brought partial relief. The patient spent a relatively quiet night, but on the morning of the second hospital day he again complained of pain, stating that the discomfort was intensified by inspiration. Physical examination at that time revealed a decrease in the intensity of the heart sounds but neither a friction rub nor a gallop rhythm was present. The lungs remained clear. The blood pressure was stable and the pulse rate had not changed significantly. The temperature had risen only to 37.8°C. During the course of the second day chest pain was fairly well controlled with narcotics except for occasional distress of pleuritic character. A later examination of the chest revealed a few fine inspiratory rales over the left posterior lung base but there were no other signs of congestion. During the evening of the second day the patient's wife was momentarily out of the room; when she returned he was lying on the floor. When questioned he could not recall the circumstances concerning his fall from bed. His skin was cold and moist and neither his pulse nor blood pressure was obtainable. There was mild cyanosis, but only a few fine inspiratory rales were heard at the posterior lung bases. Although the heart sounds were readily audible, a diastolic gallop rhythm was now detected. Despite the parenteral administration of pressor drugs the blood pressure and pulse remained unobtainable. The patient complained of nausea and vomited several times. Another electrocardiogram showed an extensive posterolateral myocardial infarction with subendocardial and anterior myocardial ischemia. As the tracing was being concluded a 2:1 auriculoventricular block was evident. The patient had a sudden grand mal seizure and expired, less than thirty-six hours after entry.

CLINICAL DISCUSSION

DR. CARL V. MOORE: Certainly most of us would agree that any physician seeing this man would have been correct in assuming that the patient had suffered an acute myocardial infarction; it would be reasonable to believe that death arose as a complication thereof. One might consider the possibility that the fall itself precipitated a complication which lead to death. Since, however, this case is being presented at a clinico-pathologic conference, perhaps one's viewpoint should be altered. In any case, I think it would be profitable to begin with the hypothesis that this patient might not have had a myocardial infarct, and consider other entities which could have explained the clinical picture. If we neglect the electrocardiogram for a moment and concern ourselves with lesions which may produce pain simulating that of coronary artery disease and myocardial infarction, a number of possibilities arise. These include dorsal root pain, dissecting aneurysm, especially at the arch of the aorta, calcific aortic stenosis, syphilitic aortitis, spontaneous pneumothorax, mediastinal emphysema, involvement of mediastinal organs, diaphragmatic hernia and acute abdominal inflammation, particularly cholecystitis, pancreatitis or rupture of a peptic ulcer. Dr. Scott, can you suggest any additions to this list, or would you care to rule out any of those which I have named?

DR. VIRGIL SCOTT: I presume that your question is directed to me particularly in respect to syphilitic aortitis. It is thought by some that syphilitic aortitis may produce substernal pain which differs from angina in being relatively constant and non-radiating. The predominant view, I believe, is that substernal pain in syphilitic aortitis occurs only when the coronary ostia are involved or if there is concomitant coronary artery disease.

DR. MOORE: Dr. Alexander, do you care to make any additions or to eliminate any of the possibilities listed on the basis of the information at hand?

DR. HARRY L. ALEXANDER: I would be perfectly willing to eliminate dorsal root pain, and on the basis of a careful physical examination, would exclude calcific aortic stenosis, syphilitic aortitis, spontaneous pneumothorax and mediastinal emphysema. I would find it hard to understand how diaphragmatic hernia, disease of the mediastinum or even acute abdominal

disease would lead to a clinical picture such as this one. On the other hand, dissecting aneurysm could certainly produce similar findings.

DR. MOORE: In other words, you would consider that our discussion is primarily an intellectual exercise, and that except for dissecting aneurysm, one need only consider myocardial infarction.

DR. ALEXANDER: I would be willing to say that if one can assume that the patient's death occurred as a complication of the illness which led him to seek medical care, only those two are of importance.

DR. MOORE: Dr. Massie, I am going to ask you to discuss the electrocardiographic findings in a moment, but would you tell us at this point whether any of the lesions which I mentioned can produce electrocardiographic changes simulating myocardial infarction.

DR. EDWARD MASSIE: No, I don't think any of them would produce enough change to be confusing. Prior to the advent of unipolar leads the situation was difficult but I do not believe that it is now.

DR. W. BARRY WOOD, JR.: May I ask Dr. Massie how he excludes dissecting aneurysm if one assumes that the aneurysm dissected proximally and involved the coronary ostia?

DR. MOORE: In that regard, of course, one would also have to include syphilitic aortitis, and perhaps calcific aortic stenosis, both of which may produce myocardial ischemia.

DR. MASSIE: It would, of course, be impossible to make an etiologic diagnosis on the basis of the electrocardiographic changes, and your point is a good one, Dr. Wood. A dissecting aneurysm which involves a coronary artery at its origin might well lead to infarction.

DR. MOORE: Among the entities which have been reported to produce electrocardiographic changes simulating those of myocardial infarction are ventricular enlargement, bundle branch block, particularly of the left bundle and myocardial ischemia. Here again one must also consider dissecting aneurysms, calcific aortic stenosis, syphilitic aortitis, myocarditis with or without pericarditis, sub-endocardial myocardial injuries, clockwise rotation, possibly pulmonary embolism, possibly low potassium and finally misapplication of the chest leads. Dr. Massie, may I ask you to evaluate this group and tell us whether the electrocardiographic changes which were observed in the present case could have been due to any of them?

DR. MASSIE: On the basis of the electrocardiographic changes, this patient's infarct was posterior in location. Most of the confusion between myocardial infarction and the various entities which you have named arises when the infarct is anterior rather than posterior. For example, left bundle branch block and left ventricular enlargement may occasionally be confusing. In left bundle branch block Q waves in leads V_1, V_2 and V_3 may suggest an anteroseptal myocardial infarction. On the other hand, leads V_5 and V_6 should enable one to differentiate the two. One cannot say, in a given case, that left bundle branch block has not resulted from a previous infarction; but if one is considering an acute change and has the benefit of serial tracings, he can be fairly sure of his ground. Left ventricular enlargement may produce very small R waves in leads V_1, V_2 and V_3 and the Q waves may be prominent, raising occasionally the question of an anteroseptal infarction but not of posterior infarct. In myocardial ischemia one sees inverted T waves in the V leads but the pathognomonic feature of muscle death, namely, Q waves, is absent. Myocarditis with or without pericarditis may complicate electrocardiographic interpretation but subsequent electrocardiographic study with clinical considerations can resolve the problem. The problem of sudden changes in the electrical cardiac position is interesting. If a patient suddenly develops clockwise rotation so that the right ventricle becomes more anterior in location, Q waves may appear in leads V_1, V_2 and V_3, suggesting an anteroseptal infarction. In pulmonary embolism such an occurrence may be encountered. In the presence of low serum potassium abnormal electrocardiographic patterns may be observed, but again the Q wave of muscle death is absent. Finally, misapplication of the chest leads should be mentioned. It is conceivable that when emergency electrocardiograms are taken in the middle of the night the placement of the electrodes may not be done with quite as much accuracy as when the tracings are taken by the regular heart station technicians during the day. If the chest electrodes are not moved far enough to the left patterns suggestive of anteroseptal infarct may be recorded; conversely, if the electrodes are placed too far to the left confusion in regard to a lateral infarct may arise. The electrocardiogram, like any other laboratory procedure, is not reliable if the faulty technics are employed.

Most of the time, however, when the electrodes are improperly placed one gets some indication which leads to suspicion. I am certain that in the present case the electrodes were placed properly, and I have no doubt but what this patient had a posterior infarct.

DR. MOORE: Would you describe briefly the electrocardiographic findings that occurred here?

DR. MASSIE: The tracings are characteristic of a posterior infarct with some lateral extension. There were Q waves in leads 2, 3 avF, V_5, and V_6 as well as inverted T waves in leads 2, 3 avF, V_5 and V_6. The tracing taken during the terminal episode showed varying degrees of block, and also showed alterations suggestive of myocardial injury, due presumably to lateral extension of the original infarct.

DR. MOORE: Dr. Edwards, do you have anything to add?

DR. JOSEPH C. EDWARDS: No, I would certainly agree with Dr. Massie's interpretation of the findings.

DR. MOORE: From what you have said, Dr. Massie, you are apparently willing to eliminate any of the possibilities included in the differential diagnosis.

DR. MASSIE: Yes, I am. I do not believe that any of the other possibilities need consideration.

DR. MOORE: Are there any questions you wish to direct to Dr. Massie?

DR. WOOD: I still believe that dissecting aneurysm with dissection into a coronary artery and subsequent infarction, cannot be ruled out.

DR. MASSIE: I should re-emphasize that while I think there is no question that the patient had a posterolateral myocardial infarction, on the basis of the electrocardiographic tracings one cannot be certain as to the exact etiology.

DR. WOOD: In that sense, then, you would be willing to consider dissecting aneurysm further?

DR. MASSIE: Yes, with dissection along the coronary artery wall.

DR. JACK BARROW: Dr. Massie, I think you mentioned that the S-T segments were elevated in the first three precordial leads of the terminal electrocardiogram?

DR. MASSIE: Yes, there was some elevation in comparison with the previous tracing in leads V_2, V_3 and V_4. The elevation was not striking and there were no Q waves.

DR. BARROW: Those changes would be compatible with pericardial effusion, would they not?

DR. MASSIE: Yes, they would.

DR. BARROW: May hemopericardium produce S-T segment elevation?

DR. MASSIE: Yes, it may. The terminal tracings are compatible with the development of hemopericardium.

DR. MOORE: Before we take up the terminal episode I would like to ask one other question. Dr. Goldman, you took care of him, and I believe you had seen him on and off during the year or two previous to his death. Do you think he had hypothyroidism?

DR. ALFRED GOLDMAN: I had not seen him professionally from the time he was hospitalized elsewhere for hyperthyroidism nine years earlier until I saw him the night prior to his admission here. I did see him socially from time to time and remember him as a very active individual. I doubt very seriously that he had hypothyroidism.

DR. MOORE: Dr. Glaser, would you hazard a guess concerning the cause of the patient's fall from bed? When he was found along side his bed after the fall he was confused. Is one justified in assuming that he had Stokes-Adams syndrome?

DR. ROBERT J. GLASER: I would consider a Stokes-Adams attack as the most likely explanation for the patient's fall. It is known that he had some degree of changing block terminally at which time he had a seizure. It might well be that the terminal episode was one of ventricular fibrillation with a Stokes-Adams attack, and it is not unreasonable to assume that his fall occurred as a result of a transient arrhythmia followed by a convulsion.

DR. MOORE: Do you have any other suggestions, Dr. Waters?

DR. HUGH R. WATERS: No, I would agree with Dr. Glaser that a Stokes-Adams attack arising on the basis of an arrythmia is the best explanation. One would also have to consider the possibility of a pulmonary embolism, particularly in view of the facts that the blood pressure was unobtainable, there were few rales in the lungs and yet the patient was cyanotic.

DR. MOORE: Among the possible courses of the terminal episode, one ought to include systemic embolism, pericarditis, possibly with effusion, rupture either of the wall of the ventricle or of the septum, ventricular aneurysm, rupture of a papillary muscle and heart failure. Dr. Massie, is this a reasonably complete list or do you care to add others? Since it is your opinion that the patient suffered a myocardial

infarction, in what order of likelihood would you list the complications of infarction?

DR. MASSIE: I recently reviewed the course of a series of patients with myocardial infarction, and among the complications which attracted my attention was rupture. It is of interest that among patients in a general hospital rupture of the heart after myocardial infarction occurs in about 9 per cent.[1] On the other hand, in a group of patients at a psychiatric institution, where there was, of course, much less cooperation on the part of the patients, rupture complicated myocardial infarction in 73 per cent of the cases.[2] Since this patient fell out of bed and was therefore subjected to excessive physical activity, rupture of the heart would seem most probable. Furthermore, pericarditis with effusion would be compatible with the electrocardiographic findings, as Dr. Barrow has already suggested, so that a strong case in support of cardiac tamponade secondary to rupture of the infarcted ventricular wall can be made. As a secondary possibility I would consider ventricular fibrillation.

DR. MOORE: If the patient had a rupture of the infarcted area, Dr. Massie, wouldn't you have expected that his heart sounds would have been difficult to hear and that he would have had the usual signs of cardiac tamponade? A house officer was at the bedside obtaining an electrocardiogram at the time the patient died. Certainly he would have recognized the signs of cardiac tamponade had they been present.

DR. MASSIE: In most cases that would be true. However, I have had two patients who died of rupture of the heart, proven at autopsy, in whom the event was so precipitous that the usual signs of tamponade were not observed.

DR. GLASER: Isn't it true, Dr. Massie, that cardiac rupture is apt to occur more commonly early in the second week following infarction?

DR. MASSIE: Rupture is most common, I believe, in the first ten days.

DR. GLASER: It was my impression that it occurs on the average between the seventh and tenth day.[3]

[1] FRIEDMAN, S. and WHITE, P. D. Rupture of the heart in myocardial infarction. Experience in a large general hospital. *Ann. Int. Med.*, 21: 778, 1944.

[2] JETTER, W. W. and WHITE, P. D. Rupture of the heart in patients in mental institutions. *Ann. Int. Med.*, 21: 783, 1944.

[3] FULTON, M. N. Acute hemopericardium: its causes and clinical manifestations. *M. Clin. North America*, 24: 1371, 1940.

DR. MOORE: Dr. Glaser, if this patient did have hemorrhage into his pericardial sac, is it conceivable that the hemorrhage was due not to rupture of the infarct but arose on the basis of hypoprothrombinemia. He had received dicumarol for only twenty-four hours prior to death.

DR. GLASER: I would doubt that, but you have had much more experience than I with the anticoagulants. What is your opinion?

DR. MOORE: I would agree that it would be most unlikely. Dr. Alexander, do you have any other suggestions regarding the cause of the patient's death?

DR. ALEXANDER: Perhaps the patient had a second infarct. One would probably not have been able to demonstrate definitive electrocardiographic changes that soon.

DR. MASSIE: Your point is a good one. The terminal electrocardiogram would have been taken too soon after the occurrence of the infarct. We did have evidence of lateral extension on the electrocardiogram taken about an hour before the patient died.

DR. EDWARDS: There is one other possibility which would have been particularly important if Dr. Goldman had told us that this patient definitely had hypothyroidism. Degeneration of the aorta with rupture occurred in a number of hypertensive patients subsequent to total thyroidectomy.

DR. MOORE: How do you reconcile the fact, Dr. Edwards, that whereas we are considering the possible relationship between hypothyroidism and coronary artery disease in this patient, there is currently much interest in the treatment of patients with coronary artery disease by making them hypothyroid?

DR. EDWARDS: There has indeed been renewed interest in the treatment of intractable angina pectoris by depression of thyroid function, particularly with I-131. The rationale of this therapeutic approach, of course, is based on the postulate that with significant lowering of the basal metabolic rate the demands on the myocardium are likewise significantly lessened; presumably the advantages outweigh the disadvantages under these conditions. In some instances, the results have been quite good.

DR. MOORE: Dr. Wood, the present era has been defined insofar as coronary artery disease is concerned, as the cholesterol-phospholipid-lipoprotein age. Assuming that this patient did have a myocardial infarction and recovered, how would you have managed him in regard

to diet? Would you have prescribed a low fat, low cholesterol diet? All of us are certainly confused by the different points of view expressed in the current literature on this subject. Dr. David Barr, in a recent editorial in the *American Journal of Medicine*, suggests that while additional "scientific analyses of diet are being attempted, a low fat, low calory diet may be advised with the expectation of partial protection against the rapid development and the complications of atherosclerosis."[4] That appears to be a conservative, wise approach at the present time.

DR. WOOD: I would certainly agree with your statement that the situation is at present confusing. As I have read the current literature I have found it difficult to make up my own mind concerning the importance of diet as far as coronary atherosclerosis is concerned. We have reviewed in previous conferences the evidence which indicates that it is difficult to influence cholesterol metabolism significantly by altering the diet. The endogenous production of cholesterol goes on at such a rapid rate that only the most stringent low cholesterol diets are apt to result in a lowering of the serum cholesterol. Had this man survived the acute episode I would not have restricted him seriously in regard to the consumption of fats. He was after all seventy years of age, and I would hesitate to complicate his life further on the basis of incomplete evidence. I would be interested to hear Dr. Massie's views on this subject.

DR. MASSIE: I am completely in agreement with you. In my opinion, the situation is not clarified to the extent that one is justified in imposing a very strict dietary regimen of this type on patients with coronary artery disease.

DR. MOORE: It is true, of course, that if one were to dine in the homes of certain leading clinicians in this country he would get neither eggs nor cream nor butter. Dr. Bercu, do you have any comments?

DR. BERNARD A. BERCU: Had I been taking care of this patient I am certain I would have made a diagnosis of myocardial infarction. Because, however, he is being presented at a clinico-pathologic conference I am somewhat more wary. Aneurysm can certainly produce chest pain similar to that described here although it is usually more sudden in onset. Nonetheless, I think that this patient probably had a dissecting aneurysm with dissection toward the heart, occlusion of a coronary artery to produce infarction and subsequent rupture and bleeding into the pericardial cavity and perhaps into the pleural cavity.

[4] BARR, D. P. The basis for dietary treatment in the prevention and control of atherosclerosis. *Am. J. Med.*, 13: 665, 1952.

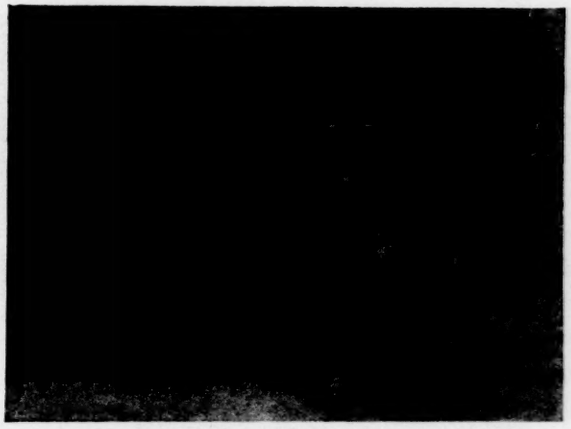

FIG. 1. The posterior wall of the apex of the left ventricle cut through the line of the rupture in the myocardium.

DR. WOOD: Dr. Bercu, although you and I are in agreement, we are probably "out on a limb."

DR. MOORE: As far as I am concerned, I think that the odds are all in favor of a myocardial infarction with terminal rupture.

Clinical Diagnoses: Myocardial infarction with terminal rupture; ? dissecting aneurysm with rupture into the pericardial cavity and pleural cavity.

PATHOLOGIC DISCUSSION

DR. EMIL FREI: At autopsy there was no dependent edema and no other significant external findings were noted. The pleural and peritoneal cavities were free of fluid. The pericardial cavity was distended by 250 ml. of fresh blood. The entire posterior surface of the left ventricle was grey-red and soft. A linear perforation penetrated the softened wall at the apex of the left ventricle posteriorly. The tract of the rupture and surrounding hemorrhage in the myocardium are shown in cross section in Figure 1. The circumflex branch of the left coronary artery was occluded by a red thrombus beginning 3 cm. from its origin and extending for 2 cm. A slight degree of arteriosclerosis was present in the aorta and coronary arteries. There was chronic passive congestion of the lungs and a moderate degree of passive congestion of the liver, spleen and kidneys.

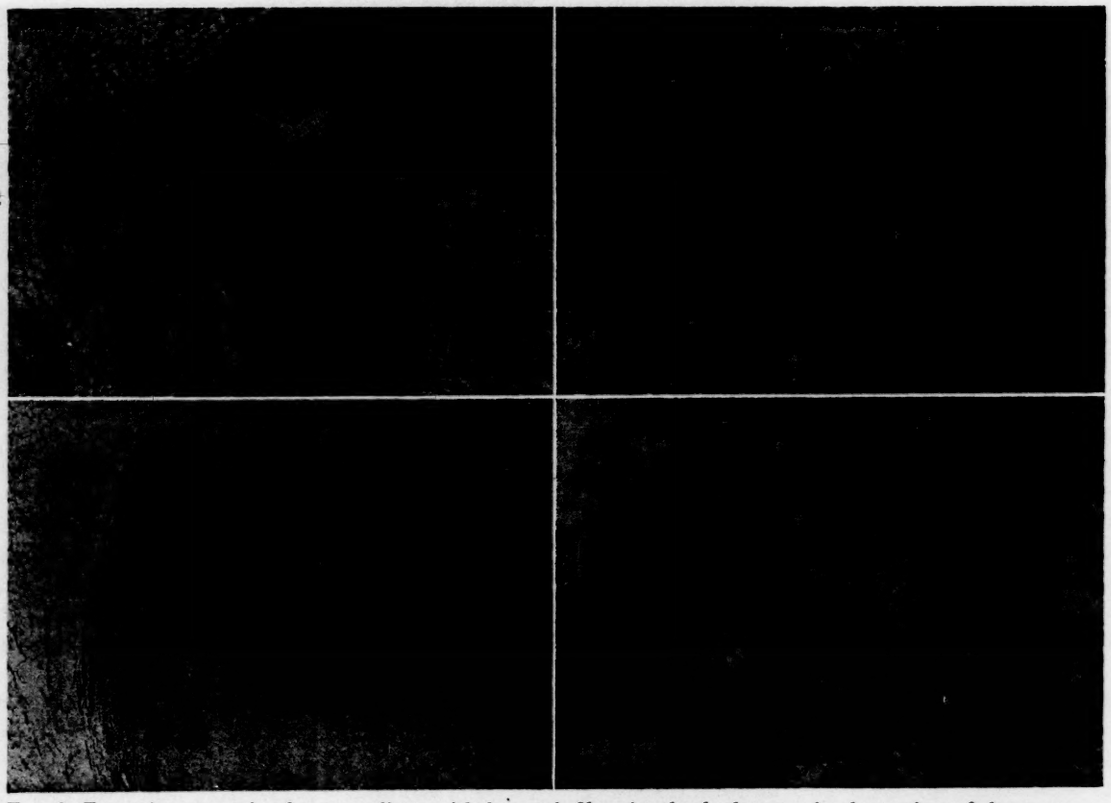

FIG. 2. Extensive necrosis of myocardium with heavy infiltration by leukocytes in the region of the rupture. Hemorrhage is also present in the epicardium and myocardium and the inner zone to the right of the illustration is necrotic muscle beyond the extent of the infiltrating leukocytes.

FIG. 3. The boundary of inward migration of leukocytes into the extensive area of total infarction.

FIG. 4. The recent thrombus which occluded the circumflex branch of the left coronary artery. Although the general degree of coronary arteriosclerosis is slight, at the site of thrombosis the artery contains an extensive plaque.

FIG. 5. A focus of fibrosis and "heart failure" cells in the lung indicative of a degree of chronic passive congestion not suggested by the clinical signs and symptoms.

DR. DAVID E. SMITH: The results of the gross examination expose the simplicity of this case. It was as straightforward an example of myocardial infarction as everyone postulated before they began to "second guess" the pathologist. The microscopic preparations do little more than confirm the gross diagnosis of a thrombus in a coronary artery, myocardial infarct and rupture of the myocardium.

Figure 2 is of a section through the myocardial infarct. This is a tangential section along the line of the tract of the rupture. The outer portion of the myocardium is necrotic and diffusely darkened at this low magnification because it is heavily infiltrated by leukocytes and hemorrhage. Much of the tissue farther away from the epicardium is also necrotic but is apparently beyond the extent of the inward migration of leukocytes. Figure 3 shows the junction between leukocytic infiltration in the infarct and muscle that is not infiltrated but shows loss of nuclei and other signs of necrosis. This boundary is very sharp. It is a result of the manner in which leukocytes must migrate from the viable tissue about the periphery of an area of total infarction and indicates the extensiveness and completeness of this particular infarct. This total infarction extends almost from the mitral ring down to the apex. The anterior wall of the left ventricle does not show changes which can be recognized as damage of an ischemic nature, nor are there any changes suggestive of hypothyroidism in the rest of the heart.

The point of myocardial rupture at the apex is typical because that is the thinnest part of the ventricular wall. The posterior site of this

rupture is a little unusual as most of them occur anteriorly rather than posteriorly, probably because anterior infarcts are more frequent and are often more complete than those of the posterior wall where a greater opportunity exists for collateral circulation between the right and left coronary arteries.

In Figure 4 there is a thrombus of recent origin occluding the left circumflex coronary artery. The general degree of arteriosclerosis in the coronary arteries was slight, but at this point of thrombosis there is a very respectable arteriosclerotic plaque which greatly narrows the lumen and provides the nidus for thrombosis. There is also anatomic evidence that this patient had appreciable cardiovascular disease of a greater degree and longer duration than was indicated by the paucity of clinical signs related in the history. Thus there was distinct arteriolosclerosis in the pancreas and kidneys. Further, the heart was hypertrophied to a weight of 480 gm.; finally, in the lungs there were a number of areas that indicated chronic passive congestion and showed thickening of the alveolar walls by fibrous tissue and many hemosiderin-filled macrophages in the alveolar lumens. These findings are illustrated in Figure 5.

In summary, this case presents an extensive and almost solitary arteriosclerotic plaque in the coronary artery of a person who has some evidence of hypertension and chronic heart failure. A thrombus formed over the plaque and caused an extensive posterolateral infarct with rupture on the third day of clinical symptoms. Note that the amount of blood recovered from the pericardium was only 250 ml. In other words, it takes only a few beats of the heart to fill the pericardium sufficiently to produce acute tamponade; and I think our findings are compatible with Dr. Massie's comments in the clinical discussion concerning the absence of signs of tamponade in some patients who die of venticular rupture. The terminal convulsion arose presumably on a basis of cerebral hypoxia; the brain was not examined and information is therefore lacking.

DR. MOORE: Dr. Massie, an electrocardiographic tracing was being taken as this man died. Did the patient stop breathing before his heart stopped, or did his heart stop first?

DR. MASSIE: I would predict that he had a seizure and stopped breathing, but that the heart beats continued for quite some time. I don't know about this particular instance with a ruptured heart, but that has been my experience in every case I have followed with a terminal electrocardiogram. I think this case exemplifies something that makes me fear the present trend of getting people up so soon after the occurrence of coronary thrombosis. This man fell out of bed, and that may have been the reason the ventricle ruptured in this instance; but I think rupture is more likely to occur if patients are ambulated before the fourteenth day.

Final Anatomic Diagnoses: Recent thrombus occluding the circumflex branch of the left coronary artery; recent infarct with rupture of the left ventricle; arteriolosclerosis in the kidneys and pancreas; chronic passive congestion of the lungs.

Acknowledgment: Illustrations were made by the Department of Illustration, Washington University School of Medicine.

Case Report

Werner's Syndrome*

With a Report of Two Cases

GLENN W. IRWIN, M.D. *and* PAULA B. WARD, M.D.
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WERNER[1] described the association of cataracts and scleroderma in four siblings in 1904. Oppenheimer and Kugel[2] reported the first two cases in the American literature in 1934 and summarized the salient clinical features which they named Werner's syndrome. Thannhauser[3] reviewed twenty-six cases including four of his own reported by 1945 and emphasizedth at the skin changes were not true scleroderma. Maeder[4] reviewed the literature and collected forty-seven cases in 1949. Since then eight additional cases have been recorded, not including the two cases in this report.[5–9]

The important features of Werner's syndrome are listed in Table I.

CASE REPORTS

CASE I. A. M., a forty-seven year old farmer, was admitted to the Indiana University Medical Center on October 19, 1950, with the chief complaint of ulceration of his feet. His growth was considered normal until he reached the age of sixteen, after which he failed to increase in height or weight. At the age of thirty-one bilateral cataracts developed and the patient had a right cataract extraction. About the same time painful callosities of the feet developed which ulcerated. For several years the ulcers would alternately heal and recur. During his early twenties the patient's hair became gray and progressive baldness ensued. He also noted progressive loss of hair over his eyebrows, face, axillae and pubic region.

Family history revealed the patient had seven siblings, none of whom had any features of Werner's syndrome. His father and mother were both normal and lived to the age of eighty-four years. There was no family history of dwarfism, cataracts, diabetes or vascular disease.

Physical examination revealed the patient to be only 5 feet tall and to weigh 90 pounds. He appeared much older than his stated age. His trunk was developed normally but his extremities were slender. His scalp hair was gray, sparse and receding. There was a left cataract and evidence of a cataract extraction on the right. Ophthalmoscopic examination on the right was essentially normal. The eyebrows were practically absent as was his beard. His nose was small and beak-shaped; his mouth was small. The skin of the face was shiny, thin and seemed taut. The subcutaneous tissue was small in amount, however, the skin was freely movable. There was slight gynecomastia. The heart was not enlarged. There was a grade I systolic murmur at the aortic area. There were no other murmurs or abnormal accentuations. The blood pressure

TABLE I
MANIFESTATIONS OF WERNER'S SYNDROME

I. Characteristic habitus and stature
   1. Short stature beginning with adolescence
   2. Slender extremities with stocky trunk
   3. Beak-shaped nose
II. Premature senility
   1. Premature gray hair
   2. Premature baldness
   3. Atrophic skin
   4. Weak and high pitched voice
   5. Arteriosclerosis
   6. Juvenile cataracts
III. Scleroderma-like changes
   1. Atrophic skin and subcutaneous tissue
   2. Circumscribed hyperkeratosis
   3. Skin tight over bones of the feet
   4. Ulcers over malleoli of ankles, Achilles tendon, heels and toes
IV. Other manifestations
   1. Tendency to diabetes mellitus
   2. Hypogonadism
   3. Osteoporosis
   4. Localized calcification
   5. Tendency to occur in siblings

* From The Department of Medicine, Indiana University Medical Center, Indianapolis, Ind.

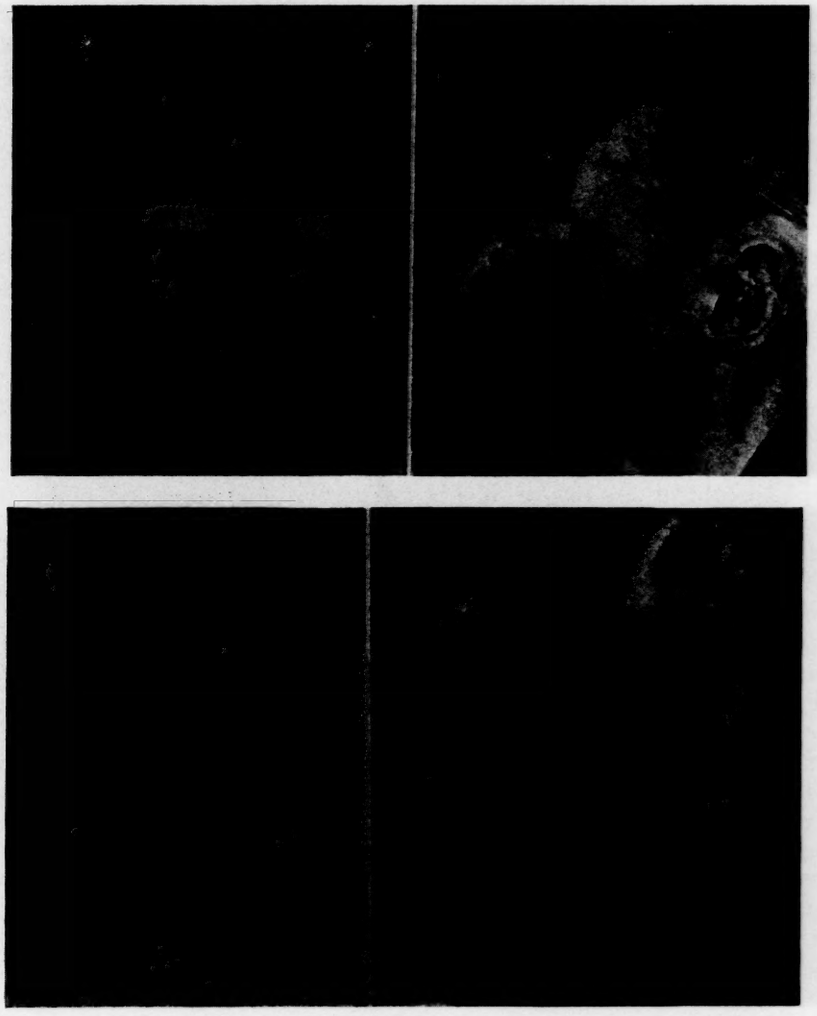

FIG. 1.

was 150/70 in both arms and the heart rate was regular and 80/minute. There was no axillary hair and the pubic hair was very sparse. The external genitalia were underdeveloped. There was atrophy of the skin, subcutaneous tissue and muscles of the lower extremities. The upper extremities were similarly involved but to a lesser degree. Areas of hyperkeratosis were present over the soles of the feet. The bones of the feet were prominent and the skin was stretched tightly over them. Large ulcers were present over both Achilles tendons and smaller ulcers were present over the internal malleoli and soles of the feet. The toes were only slightly movable because of the tight skin. The toe nails were absent except on the large toes. The terminal phalanges of the smaller toes were markedly atrophic. The dorsalis pedis and posterior tibial arteries were palpable bilaterally. Oscillometric readings were essentially normal in the lower extremities except for the feet in which they were diminished. (Fig. 1.)

Laboratory studies included a normal urinalysis and a negative blood Wassermann test. The hemoglobin was 11 gm. per cent and the red blood count was 4.6 million. The white blood count was 7,500 with a normal differential. Sedimentation rate was 5 and the hematocrit 42. Total serum cholesterol was 263 mg. per cent and cholesterol esters determination was 158 mg. per cent. Serum protein-bound iodine was 4.1 gamma per 100 cc. Serum albumin was 4.5 gm. per cent and serum globulin was 2.5 gm. per cent. Non-protein nitrogen was 32 mg. per cent. Serum chloride was 98 mEq., serum sodium was 137 mEq. and serum potassium

was 5 mEq. Serum phosphorus was 4 mg. per cent, serum alkaline phosphatase was 2.4 King-Armstrong units and serum calcium was 10 mg. per cent. After being placed on a 150 mg. calcium diet for five days the total twenty-four-hour urinary excretion of calcium was 132 mg. for one day and 141 mg. on the following day. Two basal metabolic rates were plus 5 and minus 4. The thyroid uptake of I_{131} at the end of forty-eight hours was 24 per cent. The 17-ketosteroid determination was low on two occasions and was 2.6 mg./24 hours and 5.8 mg./24 hours (method of Holtorff and Koch). The urinary reducing steroid determination was 3.0 mg./24 hours (method of Heard and Sobel). A four-hour Thorn test revealed an absolute eosinophil count of 200 before ACTH and a count of zero four hours after 25 mg. of ACTH was administered. A twenty-four-hour urinary estrogen determination was positive for 3.9 rat units and negative for 24 rat units. A twenty-four-hour urinary gonadotropin determination was positive at 12 rat units and negative for 24 rat units. A glucose tolerance test revealed the following blood sugar values: fasting, 98 mg.; half an hour, 210 mg.; one hour, 262 mg.; two hours 152 mg.; and three hours, 136 mg. Sugar, 0.2 per cent, was present in the urine at two and three hours. Ultracentrifuge studies of the serum revealed the S_f 12-20 value to be 17 mg. per cent and the S_f 20-100 value to be 56 mg. per cent. Electrocardiogram was normal.

X-ray of the chest was normal except for moderate calcification of the aorta. There was marked calcific change in the tendons of the heel and foot. Moderate calcification of the arteries of the lower extremities was noted. There was generalized osteoporosis. X-rays of the skull were normal.

Case II. E. H., a thirty-nine year old housewife, was admitted to the Indiana University Medical Center on January 9, 1952. She stated that her growth had been normal until she reached the age of thirteen to fifteen, at which time she failed to increase in height or in weight. Her mother confirmed that she had been normal until that age. At the age of thirty-four bilateral cataracts developed which were extracted. About this time the patient noted that her scalp hair became progressively sparse and her hairline had receded. She also was aware of fast heart action and a blushing of the face and neck when she became excited. This patient had had eight pregnancies, with six living children ranging in age from six to twenty-one years. During her last pregnancy she was told she had hypertension; she had much edema and convulsions occurred prior to delivery.

Family history revealed that she was the smallest person in her family. Two sisters were of normal development. The patient's twelve year old daughter was over 5 feet tall and weighed more than 100 pounds. There was no family history of cataracts, diabetes, heart or vascular disease, or shortness of stature.

Physical examination revealed her height was only 4 feet 8 inches and her weight was 80 pounds. Her upper and lower extremities were small and spindly whereas her breasts were well developed and her abdomen obese and flabby. She appeared older than thirty-nine. Her hairline receded and her hair was sparse over the scalp and eyebrows. There was evidence of bilateral cataract extraction. Ophthalmoscopic examination revealed minimal segmental constriction of the arterioles, slight increase in light reflex and minimal A-V compression. Vision was 20-30 bilaterally with correction. The patient was edentulous. The skin over the face was thin and moved freely. Her voice was high pitched and laryngeal examination revealed the mucous membrane over the vocal cords to be atrophic and thin. The lungs were normal and the heart was not enlarged. There was a grade II systolic murmur which was maximal at the aortic area. The aortic second sound was louder than the pulmonic second sound. Blood pressure was 220/70-0 bilaterally in the upper extremities and 240/110 in the legs. The pulse was regular and varied from 76 to 160/minute. The patient frequently demonstrated the flushing of face and neck, and other features characteristic of the diencephalic syndrome. After amytal the blood pressure was 110/76. Histamine, benzodioxane and regitine caused no significant change in blood pressure. There was a rectocele and cystocele. The skin over the feet was thin and moved freely over the subcutaneous tissue. There were numerous callosities but no frank ulceration. The peripheral arterial pulsations were normal. (Fig. 2.)

Laboratory studies included normal urinalyses and a negative blood Wassermann test. The hemoglobin was 11.5 gm. per cent and the red blood count was 4.05 million. The white blood count was 6,200 with a normal differential. Sedimentation rate was 44 and the hematocrit 41. Total serum cholesterol was 218 mg. per

FIG. 2.

cent. Serum protein-bound iodine was 5.2 gamma per 100 cc. Serum albumin was 4.7 gm. per cent and serum globulin was 1.9 gm. per cent. Non-protein nitrogen was 28 mg. per cent. Serum chloride was 104 mEq., serum sodium was 140 mEq., and serum potassium was 4.2 mEq. Serum phosphorus was 3.2 mg. per cent, serum alkaline phosphatase was 2.9 King-Armstrong units and serum calcium was 11 mg. per cent. After being placed on a 150 mg. calcium diet for four days the total twenty-four-hour urinary excretion of calcium was 139 mg. for one day and 126 mg. on the following day. Two basal metabolic rates were minus 6 per cent and minus 1 per cent. The uptake of I_{131} over the thyroid at the end of forty-eight hours was 29 per cent. The 17-ketosteroid determination was 14 mg./24 hours (method of Holtorff and Koch). The urinary reducing steroid determination was 2.1 mg./24 hours (method of Heard and Sobel). A four-hour Thorn test revealed an absolute eosinophil count of 154 before ACTH and a count of 21 four hours after 25 mg. of ACTH was administered. A twenty-four-hour urinary estrogen determination was negative for 4.6 rat units. A twenty-four-hour urinary gonadotropin determination was positive at 14 rat units and negative for 28 rat units. A glucose tolerance test revealed the following blood sugar values: fasting, 102 mg.; one-half hour, 198 mg.; one hour, 192 mg.; two hours, 150 mg.; and three hours, 146 mg. There was no glycosuria. Ultracentrifuge studies of the serum revealed the S_f 12-20 value to be 45 mg. per cent and the S_f 20-100 value to be 219 mg. per cent. Electrocardiogram was normal.

X-ray and fluoroscopy of the chest revealed marked calcification of the entire thoracic aorta. The heart and lungs were otherwise normal. There was minimal calcification of the vessels of the lower extremities. A barium enema, upper gastrointestinal series and intravenous pyelogram were normal except for a small esophageal diverticulum in the middle portion of the esophagus. Moderate osteoporosis of the spine was noted.

COMMENTS

The diagnosis of Werner's syndrome in general is not difficult if the physician is aware of this

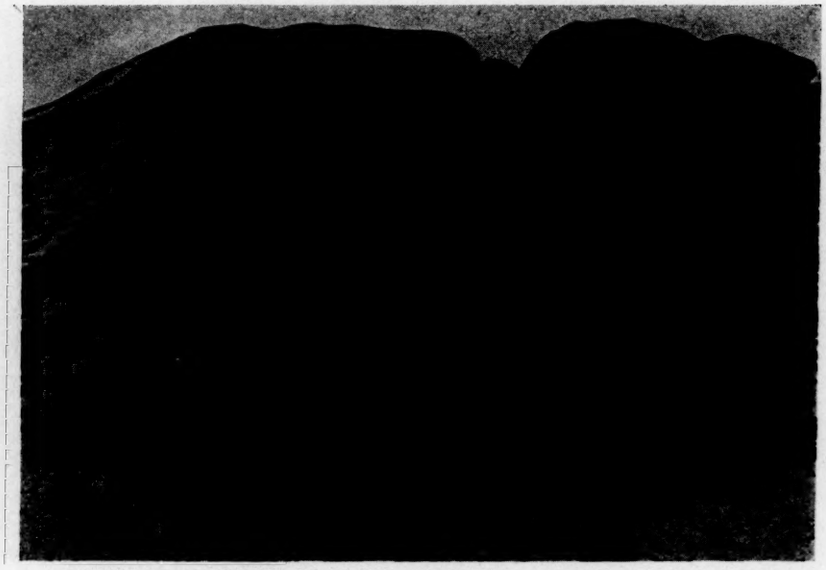

FIG. 3.

entity. Usually the general inspection of the patient's facies, premature senility and body habitus reveals the characteristic features previously outlined. Cases may be overlooked when one manifestation is predominant, and thus they may be considered cases of juvenile cataract, scleroderma, generalized arteriosclerosis or a primary endocrine disorder. An incomplete form may exist and our second case is an example in that frank skin ulceration and graying of the hair have not developed to date. Clinically our cases support the opinion of Thannhauser[3] that the skin changes are not true scleroderma. Their skin was thin but freely movable. The subcutaneous tissue especially of the face and feet was small in amount and the underlying muscle appears atrophic. Hyperkeratosis was prominent. Raynaud's phenomenon was not present. A biopsy from our first patient revealed hyperkeratosis with a decrease in size of the rete pegs. The dermis was essentially normal in thickness and the collagen bundles were loosely and disorderly arranged. (Fig. 3.) This is distinct from scleroderma in which the dermis is increased in thickness and the collagen bundles are hypertrophic and densely packed causing obliterative changes of dermal vessels.

Although several endocrine abnormalities have been associated with Werner's syndrome, there is no evidence that they are of primary etiologic significance. Diabetes mellitus is frequently associated with Werner's syndrome. In our review of fifty-five cases reported in the literature eleven patients were considered to have diabetes mellitus. Our patients did not have symptoms of diabetes or a fasting hyperglycemia, although a glucose tolerance test did indicate a mild decrease in tolerance to glucose in both cases. A determination of urinary reducing steroids (methods of Heard and Sobel) was normal for the second patient and was slightly elevated for the first patient who had the greater decrease in glucose tolerance. Clinically our cases were euthyroid and thyroid function was normal according to basal metabolic rates, serum cholesterol values, protein-bound iodine determinations and I_{131} uptake and excretion studies. The majority of the cases reported in the literature have had hypogonadism. There was clinical evidence of hypogonadism in our first case and the 17-ketosteroid determination was low. This man had mild gynecomastia, although the urinary excretion of estrogens was not high. The urinary gonadotropin excretion in this case was considered normal. Our second patient was seen during the menopause and her urinary estrogen excretion was very low and urinary gonadotropin excretion was considered within normal limits. This patient was unusual in that she had had six normal pregnancies and the menopause did not occur until about the age of thirty-eight. Usually women with Werner's syndrome menstruate for only a few years, although several cases in the literature have had multiple

pregnancies. Clinically we wondered whether adrenal cortical insufficiency existed in our patients; however, this was not substantiated by normal serum electrolytes, a significant fall in eosinophils after ACTH, absence of low urinary reducing steroids, normal basal metabolic rates and absence of flat oral glucose tolerance tests. The first patient with the low 17-ketosteroid value and the normal gonadotropin value was thought most likely to have primary gonadal insufficiency rather than adrenal cortical insufficiency. Oppenheimer and Kugel[2] believed that hyperparathyroidism might be a significant entity in this condition but this has never been substantiated. Our patients did not demonstrate a parathyroid disturbance in that repeated serum calcium, phosphorus and alkaline phosphatase determinations were normal. The urinary excretion of calcium while the patients were on a 150 mg. calcium diet was also within normal limits. Osteoporosis has been reported frequently in Werner's syndrome and was present in our two patients. Dr. John Gofman very kindly determined the values of S_f 12–20 and S_f 20–100 concentration in the sera of our patients. It is interesting that these fractions were normal for the man but were quite high for the woman. Dr. Gofman informed us that there was some evidence to suggest that the aforementioned fractions have a tendency to become lower in men after the age of sixty-five whereas in women the values tend to increase after the age of sixty-five. Physiologically our man was perhaps comparable to a man near eighty years of age.

In our cases there was no familial history of this syndrome. However, in the majority of reported cases a hereditary factor was present with a tendency for occurrence in siblings.

Effective treatment of Werner's syndrome is limited. Of course cataract extraction and management of diabetes mellitus when present are indicated. Treatment of the ulcers of the skin has not been very satisfactory. Sympathectomy has been reported as not being successful.[7] Paravertebral sympathetic blocks also have been reported as having no benefit.[5] Thannhauser[3] believed that skin grafting was at least temporarily successful. We used testosterone in our case of hypogonadism; however, there has not been significant improvement after two years.

SUMMARY

Two cases of Werner's syndrome are presented, with a discussion of the important clinical features of this entity which include short stature, premature senility, juvenile cataracts, scleroderma-like changes, skin ulcers over the feet and ankles, and certain endocrine abnormalities.

The diagnosis depends upon the physician's awareness of this entity and can usually be made by general inspection of the patient.

The etiology of Werner's syndrome is unknown. Hereditary factors seem to be important. Although endocrine abnormalities are usually present, they are variable in their occurrence and probably are of no etiologic significance.

An endocrine evaluation of our patients revealed that both had a decrease in glucose tolerance. One patient had clinical hypogonadism and both had osteoporosis. There was no evidence of primary thyroid, parathyroid or pituitary abnormality.

In both cases there was evidence of arteriosclerosis. The S_f 12–20 and S_f 20–100 values of the sera were normal in one patient and elevated in another.

Treatment is not specific and is directed toward manifestations such as cataracts, diabetes mellitus, skin ulcers and hypogonadism.

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Unusual Thoracic Manifestations in Filariasis Due to Loa Loa*

Results of Treatment with Hetrazan and Naphuride Sodium

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ENDEMIC only in parts of Africa, filariasis caused by the nematode Loa loa is rarely observed in this country. We recently had opportunity to study a patient with this disease and report our findings since an unusual clinical picture was encountered and some interesting results followed treatment with hetrazan® (1-diethylcarbamyl-4-methylpiperazine hydrochloride) and naphuride sodium.®

Human infection with Loa loa occurs chiefly along the west coast of equatorial Africa. The disease is common in Nigeria, the Anglo-Egyptian Sudan, French and Belgian Congo and Ungola.[25] Man is infected with the parasite by the bite of the insect vector, the blood sucking mangrove fly, Chrysops dimidiata. While feeding the female flies deposit the larval worms on the skin. The latter quickly penetrate into the subcutaneous tissues where they mature into adults in about four months. The adult females give birth to microfilariae which enter the blood stream and infect the blood sucking insects. In the fly the microfilariae migrate from the stomach through the thoracic muscles to the proboscis.

The worms develop very slowly in the human host. About four years elapse between the time of infection and the appearance of the next generation of microfilariae in the blood. The adults live in and move freely through the loose connective tissues. They are about 1.5 inches in length and resemble small white threads. The microfilariae are about 300 micra in length and are found in the blood in greatest numbers during the day, in contrast to the nocturnal periodicity of the microfilariae of Wuchereria bancrofti.[28]

In many patients with the disease the worms can be seen and felt beneath the skin. They often appear beneath the conjunctivae where they cause severe pain, chemosis and lacrimation. In the subcutaneous tissues the worms may move several inches in a few minutes.[12]

Allergic reactions to the parasites give rise to recurring subcutaneous and intramuscular swellings and nodules called "Calabar swellings," after a town in Nigeria where loiasis is common.[12,14–16] They may occur on any part of the body surface but are most common on the forearms. They are usually 1 or 2 inches in diameter and may persist for about five days. As a rule they are attended by itching and burning, rarely by pain. When they occur frequently in the same area chronic cystic tumors may be formed. These are often attached to the tendon sheaths and muscular aponeuroses and contain straw-colored fluid.[28]

Involvement and obstruction of the lymphatics by the adult worms occurs but is not as frequent as in infections with Wuchereria bancrofti. Severe lymphatic edema, lymph varix, hydrocele and varicocele have been noted in the hyperendemic areas.[12] Eosinophilia is a common hematologic finding.

CASE REPORT

A thirty-one year old Negro male was admitted to the Second Medical Service (Dr. I. Snapper) of The Mount Sinai Hospital on June 15, 1951. He complained of chills and fever for two days and a painful mass in the left pectoral region for one week.

In 1946 a painless, slightly raised swelling, about the size of a fist, was noted on his chest below the left clavicle. He was examined at Harlem Hospital in New York City and a four-plus positive serologic reaction for syphilis was found. He was treated for lues for a period of two years with injections of bismuth and

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arsenical preparations. He did not receive penicillin. During this interval the swelling on his anterior chest wall fluctuated in size but never caused any discomfort. It disappeared completely for variable periods of time. In 1950 he developed a dry cough. X-rays of his chest revealed a large mass in his mediastinum and he was advised to enter a hospital for observation. However, he declined to do so and continued to work as an elevator operator.

He was born in Nigeria and lived there until 1941. At that time he got a job as a steward abroad a British merchant ship. In 1945 he came to New York City where he has lived since. Aside from several attacks of acute urethritis, his health in Nigeria was good.

On examination the patient was found to be a well nourished and developed Negro male who had a slight cough productive of small amounts of mucoid sputum. The body temperature (rectal) was 101.2°F., the pulse rate was 104, respiratory rate 24 and the blood pressure was 145/100. The trachea deviated to the right and was freely movable. The neck veins were flat. There were several hard, discrete, non-tender almond-sized lymph nodes in each axilla.

The striking physical finding was an elevated, fluctuant, tender swelling of irregular outline covering the left pectoral region. It extended from the lower margin of the pectoral muscles to the anterior border of the trapezius and from the left sternal border to the anterior axillary line. On recumbency the non-pulsatile mass diminished in size and a fullness appeared in the left supraclavicular fossa. At the inferolateral border of the mass there was a hard, fixed, non-tender nodule (2 by 3 cm.). There were similar but smaller nodules at the superolateral and superomedial borders. Dullness and diminished breath sounds were noted at the base of the left lung posteriorly and over the left anterior chest from the second to fourth ribs parasternally. The liver was percussed one fingerbreadth below the costal margin. There were no other palpable abdominal organs or masses.

The hemoglobin concentration of the blood was 13.0 gm. per cent. The white blood count was 16,000 per cu. mm. The differential count was 67 per cent segmented, 16 per cent non-segmented polymorphonuclear leukocytes, 5 per cent lymphocytes and 7 per cent eosinophils. The platelet count was 100,000. Blood Wassermann and Kahn tests were negative. The erythrocyte sedimentation rate was 109 mm. in one hour (Westergren). Urinalysis was negative for sugar, albumin and formed elements. Blood culture was negative. A search for Hargrave's cells in the blood was negative. Blood urea nitrogen was 14 mg. per cent, blood sugar 105 mg. per cent, blood uric acid, 3.6 mg. per cent, serum alkaline phosphatase, 5 K-A units, serum total protein, 6.6 gm. per cent, albumin, 3.6 gm. per cent and globulin 3.0 gm. per cent.

Fluoroscopy and an x-ray of the chest revealed a large, dense, homogeneous, sharply demarcated mass, about 8 cm. in diameter, situated in the anterosuperior region of the left chest and extending slightly into the right lung field at the level of the aortic arch. The trachea was deviated to the right and there was a small pleural effusion at the left base. (Figs. 1 and 2.) The mass did not pulsate. There was no delay in the passage of barium through the esophagus.

Bronchoscopy revealed narrowing and distortion of the left main bronchus particularly from the anterior aspect. There was no demonstrable intrabronchial abnormality. Biopsy of a left axillary lymph node showed the changes of chronic non-specific inflammation. Examination of the sternal bone marrow showed mild plasmacytosis but the marrow was otherwise normal. An intradermal skin test with Echinococcus antigen was negative.

A biopsy obtained from the wall of the center of the mass showed huge dilated channels measuring approximately 0.5 cm. in diameter from which a profuse amount of straw-colored fluid drained. Microscopically, the specimen had the appearance of inflamed cystic hygroma.

In an attempt to determine whether the cystic chest wall mass communicated with the deeper lymphatics of the thorax the patient was given a fatty meal containing Sudan III and the superficial swelling was then aspirated. The fluid obtained contained blood and autolysed cells but no dye-stained particles were seen.

Although it was now possible to classify the chest wall mass histologically, the problem of the nature of the mediastinal tumor and its possible relation to the former remained unsolved. Because of the patient's birth place and the lymphatic nature of the superficial mass, the possibility of filariasis was considered. However, microfilariae were not found in the peripheral blood.

It was thought that the mediastinal tumor was either a lymphoma or a cavernous lym-

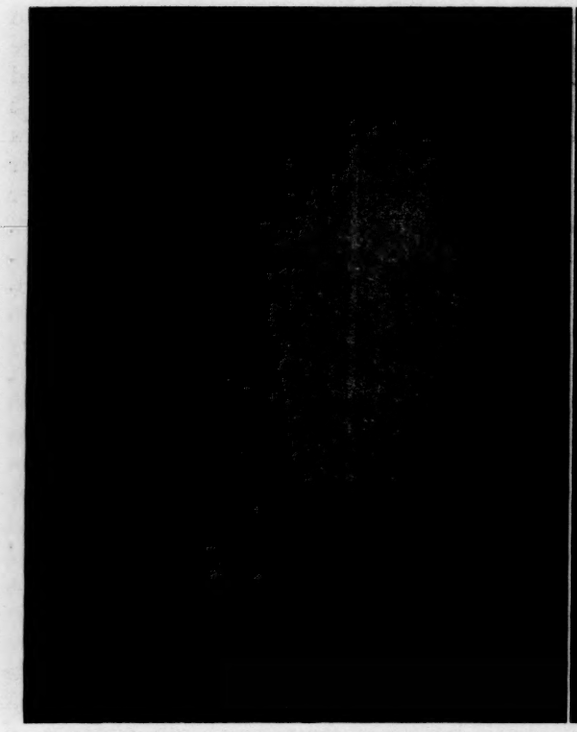

FIG. 1. Anteroposterior radiograph of the chest, showing a large, dense sharply demarcated mass in the left upper chest and extending into the right upper chest.

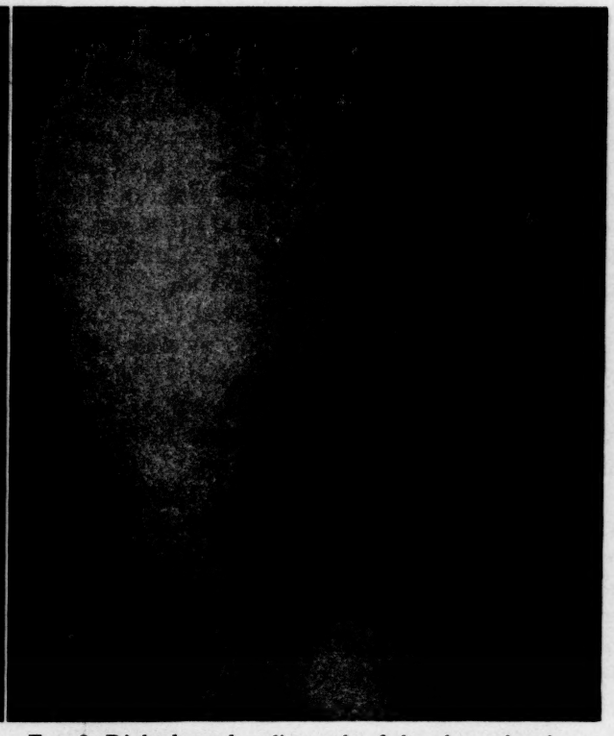

FIG. 2. Right lateral radiograph of the chest showing anterior superficial mass and a dense mass in the superior mediastinum.

phangioma involving the left side of the neck, the anterior mediastinum and chest wall. A course of radiotherapy was decided upon. After one week of therapy the chest wall mass was smaller and the nodules could no longer be palpated within it. Treatment was therefore continued for an eleven-week period in the outpatient clinic; the patient received a total of 2,500 r to a 20 by 20 anterior field, 2,500 r to a 15 by 17 posterior field and 600 r to a 15 by 10 left lateral chest field. Upon completion of radiotherapy the mediastinal mass was slightly smaller but the left pleural effusion had increased.

Second Admission. The patient remained asymptomatic for eleven weeks. He then developed a second episode of sharp left anterior chest pain, shaking chills, fever and progressively increasing cough. On readmission to the hospital examination showed the chest wall mass to be somewhat smaller than on the first admission but it was still warm and fluctuant. The liver edge was palpable 5 cm. below the costal margin. It was blunt, smooth, firm and nontender. The tip of the spleen was just palpable. Fluoroscopy of the chest disclosed a marked increase in the size of the shadow at the base of the left lung.

The left pleural cavity was tapped and 750 cc. of serosanguineous fluid were obtained. After centrifuging the supernatant was amber colored and translucent. The specific gravity was 1.019. The Rivalta test for globulin was positive and the protein concentration was 9.75 gm. per cent. Microscopic examination revealed 84,000 erythrocytes and 250 mononuclear leukocytes per cu. mm. Smears failed to reveal the presence of acid-fast bacilli and cultures of the fluid were sterile. Examination for fat revealed only a small amount of neutral fat. The number of eosinophils in the peripheral blood varied from 5 to 10 per cent in successive blood counts.

Four days later a second thoracentesis was performed, about twelve hours after the patient had had a fatty meal containing the dye, Sudan III. About 600 cc. of bloody fluid were removed from the left pleural cavity. Microscopic examination of the fluid failed to reveal the presence of fat droplets or fatty acid crystals stained with Sudan III. However, large numbers of actively motile microfilariae were seen. The

latter were easily found in drops of capillary and venous blood.

One cc. of blood was laked in 9 cc. of 2 per cent formalin solution.[14] After centrifuging and washing with tap water the sediment was smeared on slides and fixed in dilute acetic acid. The smears were then mordanted with 4 per cent ferric ammonium sulfate and stained with iron-hematoxylin. The microfilariae appeared stiff and angular. Each possessed a sheath and nuclei that extended to the tip of the pointed tail. (Fig. 3.) On the basis of these characteristics the microfilariae were identified as Loa loa. Blood samples taken at various times during the day and night and concentrated by the above method failed to reveal any other species, such as Microfilaria perstans or bancrofti. Microfilaremia was most marked during the day and the greatest number of organisms was found in the blood at mid-day. A few microfilariae were found in the blood at 7:00 P.M. and 1:45 A.M.

Treatment with hetrazan (1-diethyl carbamyl-4-methylpiperazine hydrochloride) was begun. The initial dose of 50 mg. per day was gradually increased to 300 mg. by the end of the first week of therapy. The patient tolerated the drug well and a gradual decrease in the number of circulating microfilariae was observed. However, the larvae did not disappear from the blood until the tenth day of treatment.

Third Admission. While hetrazan was continued the patient remained fairly well for six weeks. Then he developed a third attack of fever, pain in the chest, dyspnea and swelling of the mass in the left anterior pectoral region. On reexamination the anterior lesion was warm, fluctuant and tender. It was approximately the same size as on the first admission to the hospital. However, x-rays of the chest showed a decrease in the size of the mediastinal mass, which was more radiolucent than before. Its borders, which had previously been convex and smooth, were now concave and scalloped in appearance. The shadow at the base of the left lung had increased in size. (Figs. 4 and 5.)

Two thoracenteses were performed below the angle of the left scapula and yielded 750 cc. and 520 cc., respectively, of opaque, milky fluid. Smears of the fluid stained with Sudan III showed numerous fat globules on microscopic examination but no microfilariae were found. The appearance of fat in the pleural fluid (chylothorax) and the decrease in the size of the mediastinal mass suggested that a cystic dilatation of the thoracic duct or one of its tributaries (lymph varix) had ruptured into the left pleural cavity. The patient's dyspnea was much relieved after removal of the pleural effusion. The daily dose of hetrazan was increased to 450 mg. and he was discharged once again to be followed in the outpatient department.

Fourth Admission. Six weeks later, during the thirteenth week of therapy with hetrazan, he had another attack of pain in the left anterior chest, a shaking chill and fever. On admission to the hospital his temperature was 103°F. (rectal) and the mass on the left pectoral region was warm, tender and fluctuant. The appearance of the chest on x-ray was similar to that on the last admission. Thoracentesis yielded 100 cc. of bloody chylous fluid from the left pleural cavity. No microfilaria were found in this fluid but one of eight blood samples examined after laking and centrifuging revealed a few microfilariae.

Although treatment with hetrazan had almost completely eliminated microfilariae from the blood for a period of thirteen weeks, the patient's general condition was unchanged. He complained of dyspnea, malaise and was unable to work. It was believed that viable adult nematodes might be responsible for the recurring acute exacerbations of fever, chest pain and swelling of the mass on the anterior chest. It was decided to administer intravenous injections of naphuride sodium, a trypanosomicidal agent which has been shown to be lethal for the filarial worm, Onchocerca volvulus. Accordingly, hetrazan was discontinued and a test dose of 300 mg. of naphuride sodium was given intravenously. This was followed by eight 1 gm. doses injected at weekly intervals. The patient was ambulatory for the last month of this course. The therapy was well tolerated and was unattended by toxic manifestations.

Following the use of naphuride sodium the patient's general condition improved. During an eleven-month period of observation he gained 20 pounds and had no more of the acute febrile episodes that were responsible for his four admissions to the hospital. The swelling on his anterior chest wall disappeared completely. However, he occasionally noted short periods of malaise associated with aching and stiffness in his extremities. X-rays of his chest showed a further decrease in the size of the mediastinal mass and in the extent of the

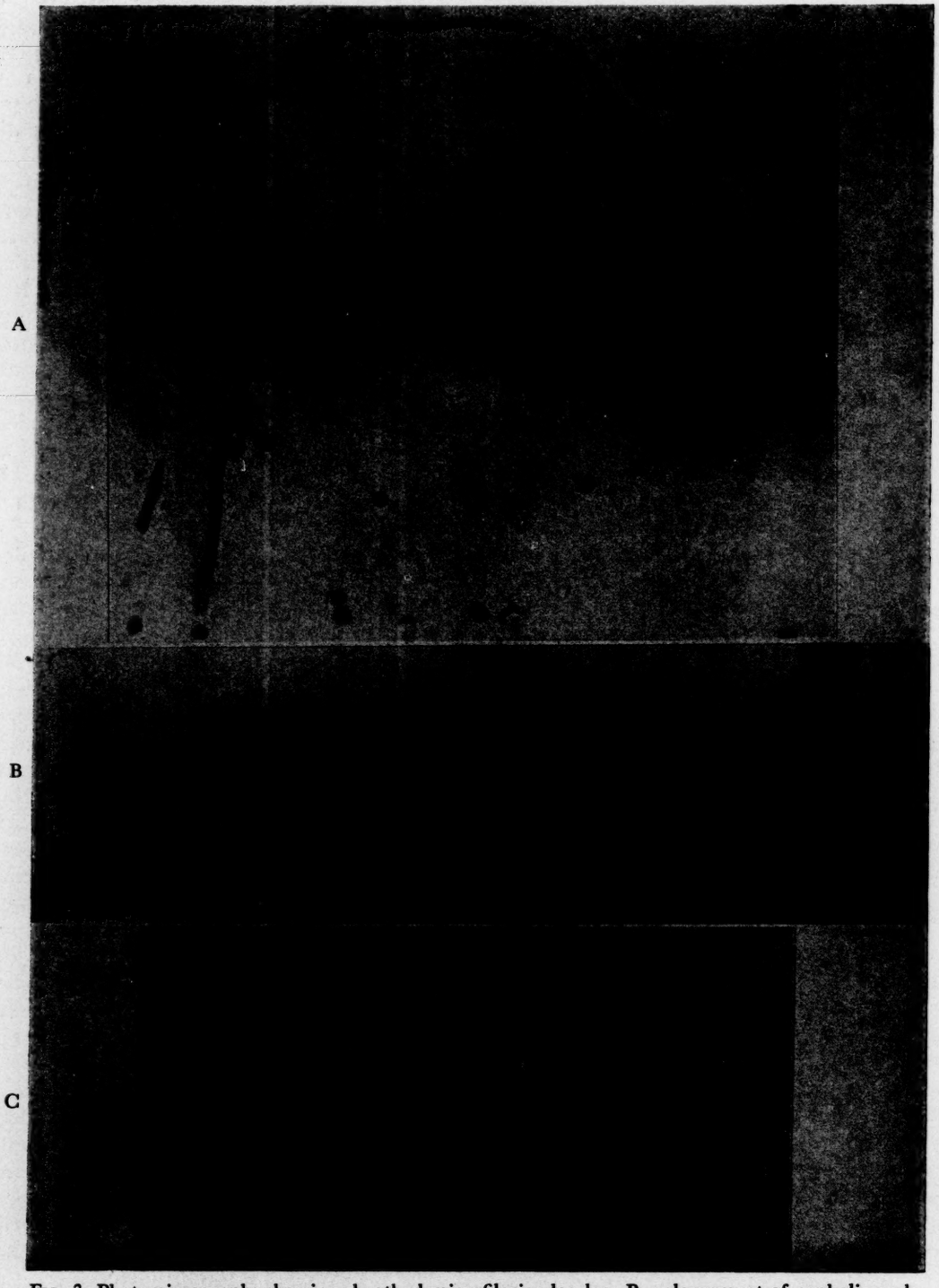

FIG. 3. Photomicrographs showing sheathed microfilariae loa loa; B, enlargement of cephalic end; C, enlargement of caudal end.

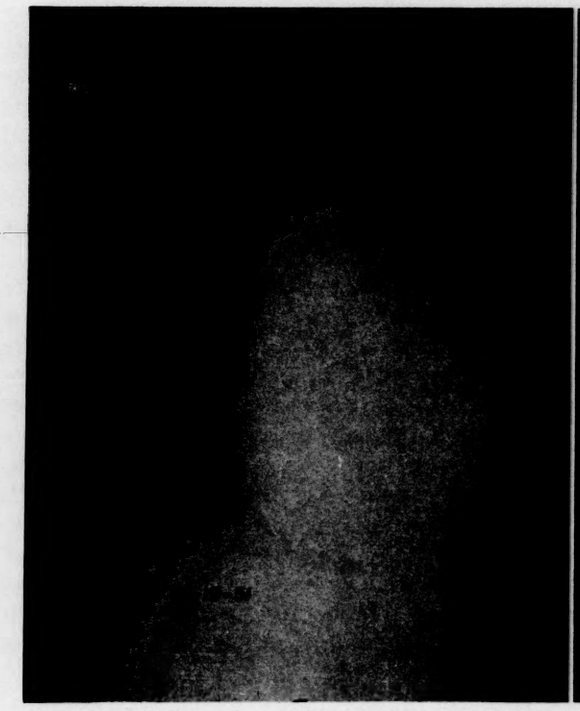

FIG. 4. Anteroposterior radiograph of the chest (December 19, 1951) showing a decrease in the size of the mass in the left upper chest and an increase in shadow at the left base.

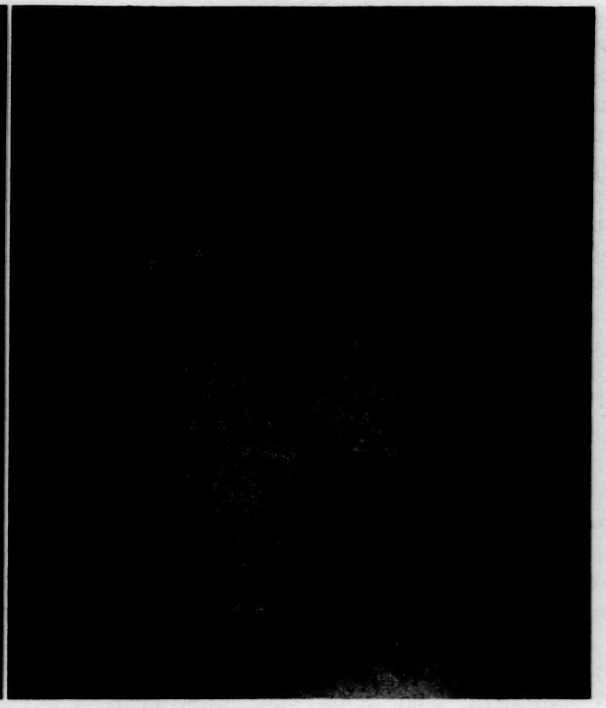

FIG. 5. Right lateral radiograph of the chest (January 1, 1952) showing a decrease in shadow in the upper anterior mediastinum and a prominent superficial anterior swelling.

shadow at the base of the left lung. (Fig. 6.) Examination of the blood revealed a persistent moderate eosinophilia (10 per cent) and occasional Microfilariae loa.

COMMENT

The occurrence of the thoracic manifestations that comprised the striking clinical feature of the above case has apparently not been previously described in loiasis. Despite a review of the literature dealing with this disease and the other forms of filariasis, we were unable to find a reference to a similar case.[1,4–7,12,15–17,19,22,27,28,32,35]

In fact, although filariasis was usually mentioned as a cause of chylothorax in many of the reviews of the latter condition, there appear to be no published clinical or pathologic accounts of filarial chylothorax.[2,11,20,29,37]

Whether or not loiasis was the cause of the mediastinal mass and of the chylothorax cannot be determined from our studies since pathologic examination was impossible. However, the following points seem to favor an etiologic relationship. Microfilariae were so abundant in the pleural fluid obtained during the second hospital

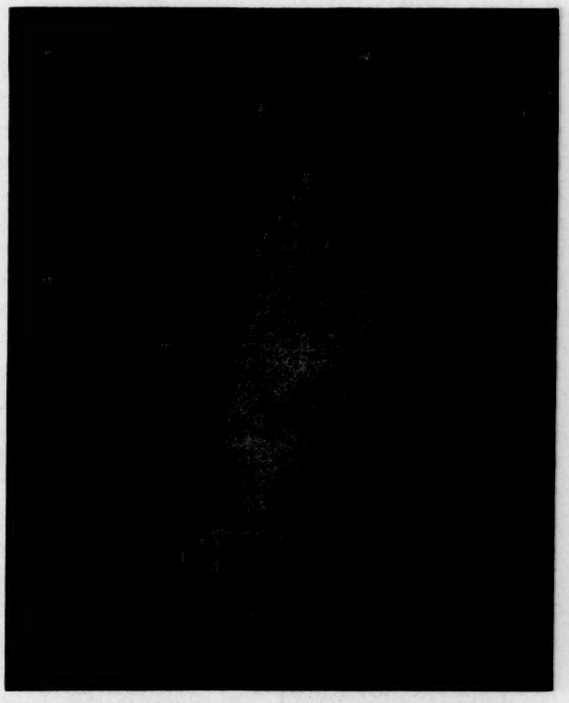

FIG. 6. Anteroposterior radiograph of the chest showing further decrease in shadows in the left upper and left lower lung fields (October 3, 1952).

admission that it is reasonable to attribute their presence to the localization of adult worms in the mediastinum. Froes reported the finding of numerous microfilariae in the ascitic fluid in a case of Bancroftian filariasis with ascites.[28] The appearance of chyle in the pleural fluid and the concomitant shrinkage of the mediastinal mass suggested that the latter was a lymph varix, arising from the thoracic duct, that had ruptured and spilled its contents into the pleural cavity. It is conceivable that the Loa loa adults could produce obstruction of the thoracic duct or one of its tributaries in the mediastinum. The worms have been known to cause lymphatic obstruction and lymph varices in the inguinal regions and at autopsy they have been found in every part of the body including the heart and pericardium.[12,28] Tissue reactions to the microfilariae have been observed by Klotz who found them within fibrotic nodules in the spleen and other tissues.[13]

In filariasis due to Wuchereria bancrofti instances of obstruction and extreme dilation of the thoracic duct below the diaphragm have been described in several reports.[27] Young found an enormous retroperitoneal lymph varix and a greatly dilated thoracic duct in a case of chyluria. Among nine other cases of filarial chyluria collected from the literature by Stephens and Yorke there were three in which obstruction and dilatation of the retroperitoneal portion of the thoracic duct was observed at postmortem examination.[27] Wise reported the finding of a large chylous cyst between the two layers of the mesentery in a case of ascites and also described an abdominal lymphangiovarix containing adult worms in some of the varices.[27]

In our case the recurrent swelling on the left pectoral region had the characteristics of a cutaneous lymph varix. The periodic acute inflammatory reactions within it were in all likelihood episodes of filarial lymphangitis.[19] The disappearance of this mass after the chemotherapy of the loiasis is in favor of its filarial etiology.

It is possible that this patient had two independent conditions, namely, loiasis and a cystic lymphangioma of the mediastinum and anterior chest wall. Loiasis has been known to occur in the absence of clinical manifestations and our patient never experienced some of the common symptoms of the disease, i.e., the movements of the live worms beneath the skin and the occurrence of the typical migratory calabar swellings. A cavernous lymphangioma was found by Neuhof and Swift in a patient with a soft cystic swelling in the left supraclavicular region and a large left pleural effusion.[29] Chyle was obtained from the mass and from the pleural cavity. Exploration of the left supraclavicular region disclosed a diffuse, fatty mass behind the clavicle. Biopsy revealed this to be a lymphangioma.

Hetrazan (1-diethylcarbamyl-4-methylpiperazine hydrochloride) was shown to have a marked filariacidal action in Bancroftian filariasis by Santiago-Stevenson et al.[23] Oral administration of the drug caused a rapid disappearance of microfilariae from the blood and favorably affected the course of the disease. Subsequently, encouraging therapeutic results with hetrazan were reported in loiasis and onchocerciasis.[3,18,24,26,30,32] The drug was effective against the microfilariae volvulus and loa in man in doses comparable to those used in W. bancrofti infections but had no effect on microfilariae perstans or ozzardi.[10]

In loiasis the use of the drug has been attended by prompt cessation of the Calabar swellings and clearing of the blood of microfilariae within a week. Murgatroyd and Woodruff[18] treated nine patients with doses of 2 to 6 mg. per kg. for periods of from ten to twenty-one days and observed recurrence of symptoms in only one case during a six-month period of observation. Shookoff and Dwork[24] treated five cases with 300 mg. a day for seven to ten days. Four patients were relieved of Calabar swellings for four to ten months. Prior to treatment none of the group had had symptom-free intervals for more than two months. Stefanapoulo and Schneider[26] treated twenty patients with 3 to 6 mg. per kg. per day for seven to ten days. In nineteen patients all symptoms disappeared within forty-eight hours. In most of these cases symptoms recurred several weeks after the cessation of therapy but they were less severe.

Reactions, supposedly of an allergic nature, have occurred during the early stages of treatment with hetrazan and it has been advised that treatment be begun with small doses. The common untoward reactions have included nausea, vomiting, fever, diarrhea, pruritus, morbilliform and papular skin eruptions. The mode of action of the drug on the adult Loa loa is not known and there is no evidence that the worms are killed by it even when given for prolonged periods. Woodruff[36] postulated that

the drug acts as an opsonin, sensitizing the microfilariae to the phagocytic activity of the cells of the reticulo-endothelial system.

In our case, although hetrazan was given continuously for thirteen weeks in doses up to 7 mg. per kg. per day, the blood was not completely cleared of microfilariae and there was little change in the general condition of the patient. The mass on the anterior chest wall persisted and was the site of repeated acute inflammatory flare-ups. This clinical behavior was attributed to the presence of live worms and their toxic products and to repeated secondary infections of the obstructed lymphatics. Beye and his co-workers[1] observed that continuous treatment of W. bancrofti infections for more than one year did not reduce the frequency of recurrent attacks of acute filarial lymphangitis.

The use of naphuride sodium in this case was prompted by the recent report that it had a lethal action on Onchocerca volvulus.[3,34] In 1926 Chopra and Rao[31] tried this drug in two cases of W. bancrofti infection and failed to observe an effect on the microfilariae with the small doses that they used. The drug was well tolerated by our patient. The change in the clinical course and the general physical improvement that was observed during the eleven-month period following its use suggested that it may have been of value in reducing the number of live nematodes in this case.

Naphuride sodium is a toxic substance and may cause adrenal or renal damage.[9,33] It is slowly eliminated from the body and has a cumulative action. The initial dose should not exceed 300 mg. intravenously because of possible idiosyncrasy. One gm. can usually be administered safely, intravenously, once a week until a total of 10 gm. has been administered. The reported toxic effects include chills, fever, headache, nausea, pruritus, conjunctivitis, stomatitis, purpura, hemoglobinuria and agranulocytosis.

SUMMARY

1. A case of loiasis is reported in which a lymph varix of the chest wall, a mediastinal tumor and a chylous pleural effusion were observed.

2. Treatment with hetrazan for thirteen weeks failed to clear the blood of microfilariae and did not prevent acute exacerbations of fever and painful swelling of the lymphogenous mass on the chest wall.

3. Treatment with naphuride sodium was followed by the cessation of acute exacerbations, disappearance of the chest wall mass and a 20 pound gain in weight during an eleven-month follow-up period.

Acknowledgment: The authors wish to express their indebtedness to Dr. I. Snapper for his advice in the diagnosis and treatment of this case. We also wish to thank Mr. Fred Lazarus for his technical assistance in the demonstration of the morphology of the microfilaria. The naphuride sodium used in this case was supplied generously by the Winthrop Chemical Company.

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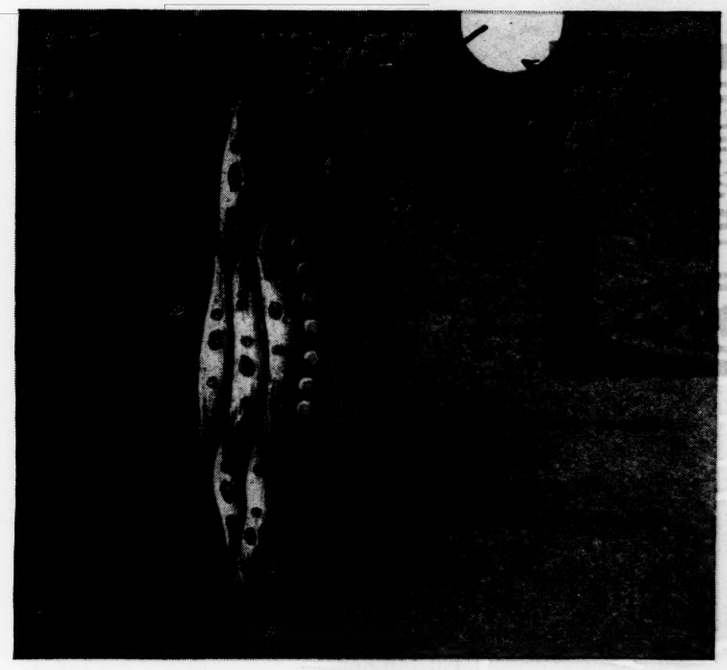

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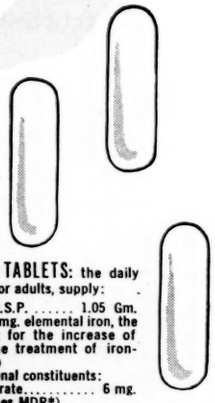

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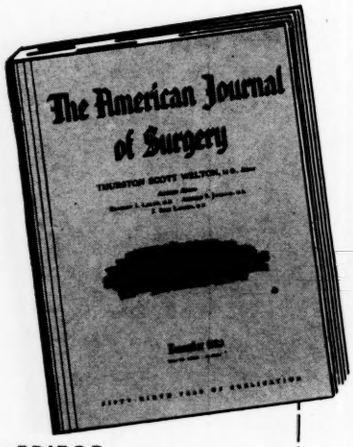

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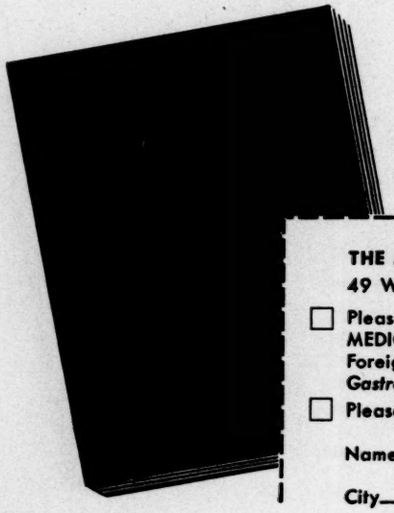

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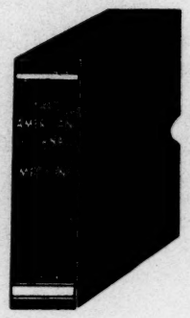

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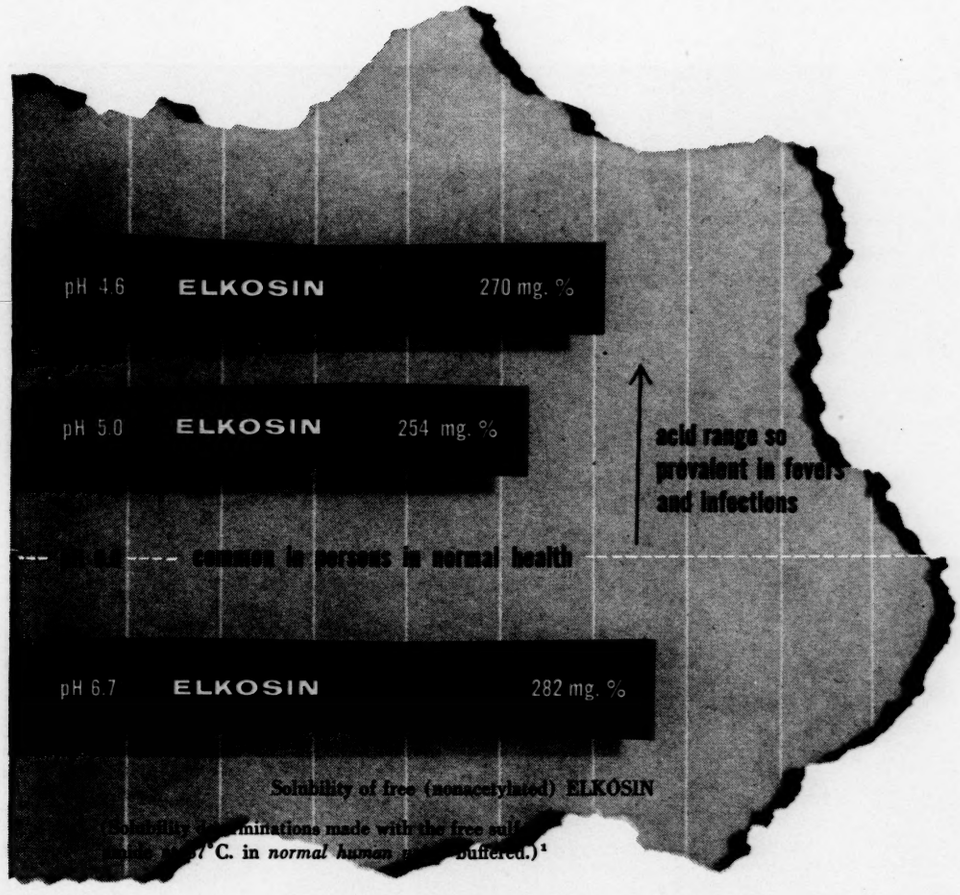
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1. Ziegler, J. B.; Bagdon, R. E., and Shabica, A. C.: To be published.

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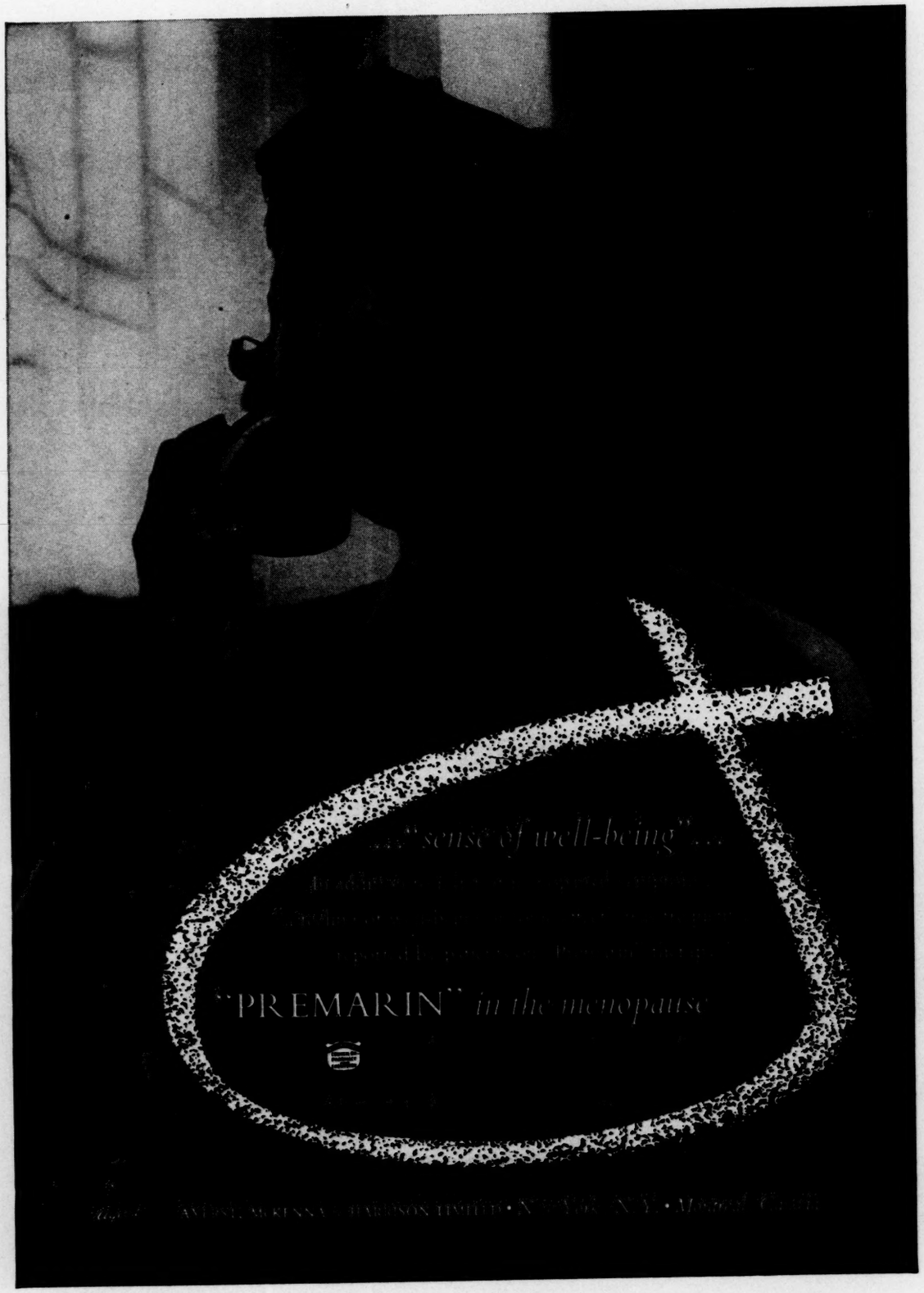
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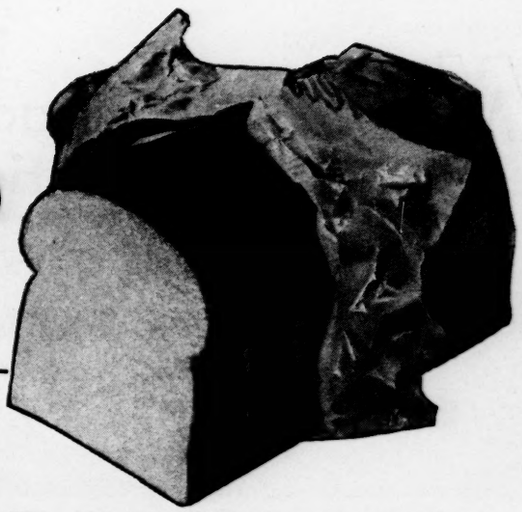

Some twelve years ago the baking industry began large-scale, nationwide commercial production of enriched breads. Today such breads represent about three-fourths or more of all the marketed white bread in the United States,[1] and rank high among the foods which contribute essential nutrients—in important amounts—at low cost—to the nutrition of the American people.[2]

It is not so long since deficiencies of certain B vitamins and iron were regarded as sufficiently widespread in the United States to merit serious attention. By providing broad distribution of these important nutrients in effective amounts, commercial enriched breads have contributed notably to reducing the incidence of these deficiencies,[1] as reported for instance among patients of charity clinics throughout the country.[3] It is authoritatively believed that the enrichment of bread has improved the health of a large segment of our population.[4]

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*Daily dietary allowances recommended by National Research Council for a sedentary man (154 lb.).

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1. Geddes, W.F.: Cereal Chemists Guard Nutrition, Agricultural and Food Chemistry *1*:38 (Apr.) 1953.
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7. Watt, B.K., and Merrill, A.L.: Composition of Foods—Raw, Processed, Prepared; United States Department of Agriculture Agriculture Handbook No. 8, 1950.

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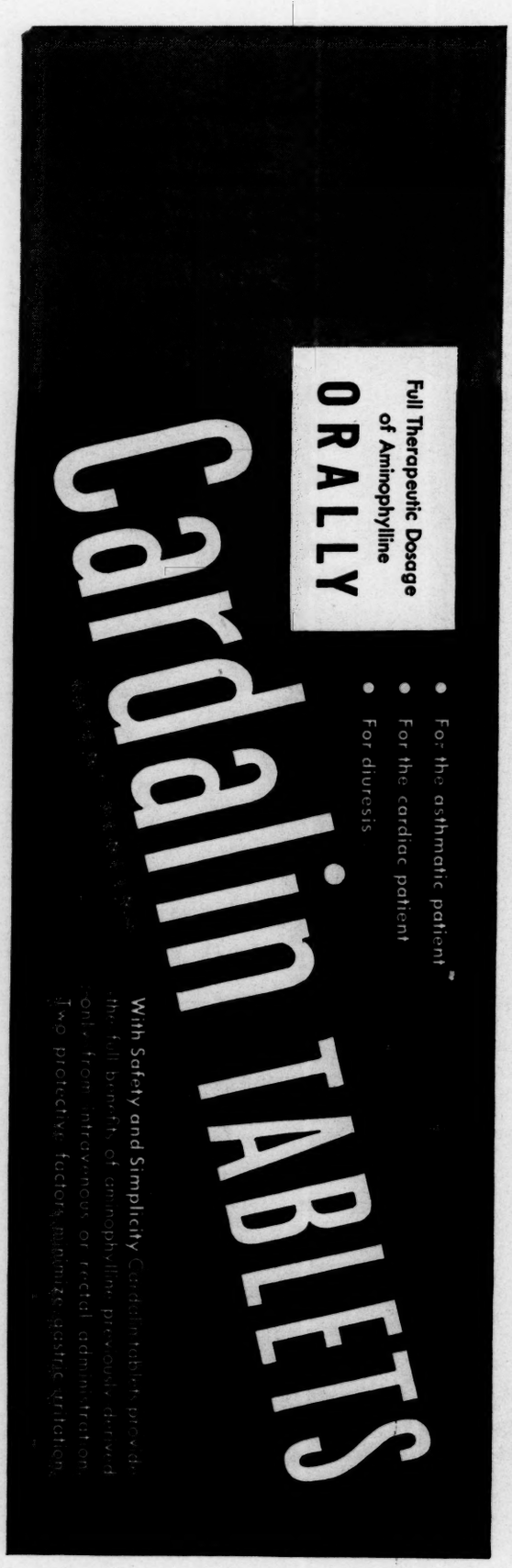
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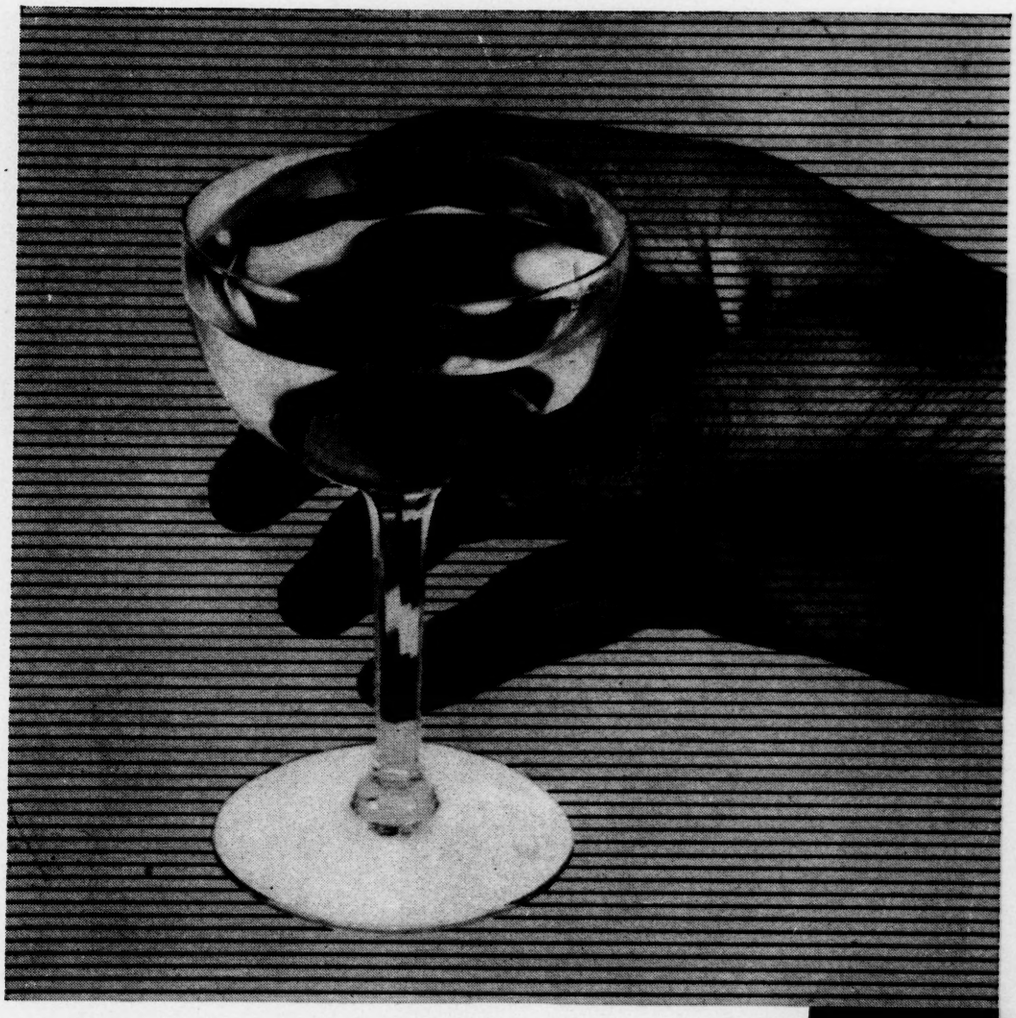

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